Harvard Medicine

AUTUMN 2013

Handed Down

Medicine illuminates the bonds between generations

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SWEET SORROW: Leaving Austria following the Nazi occupation was a difficult decision for Sigmund Freud and his daughter Anna, but once made, they acted swiftly, a move that allowed Max Schur, Freud's physician, and his family to plan their own departure.

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From the Dean

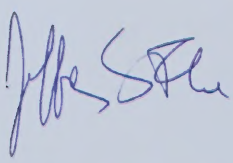
THOUGHTS ON INNOVATION

ROOTS RUN DEEP at Harvard Medical School, both those of the School as a centuries-old institution and those linking alumni and students. The story of HMS is chronicled in its families—the Shattucks, the Richardsons, and the Warrens, to name a few—who have made lasting contributions to the School and to its mission to advance medical education and biomedical research. These contributions continue, if not directly through the founding families, then through the new families and future legacies that are seeded within each incoming class.

Harvard Medicine looks at the facets of legacy in this issue, exploring what can be handed down from one generation to the next. We talk with researchers who scour the genomes of families in search of clues to inherited conditions, and with other scientists who explore the influence that speech, as articulated by parents and others, has on an infant's ability to acquire language.

We also take time to listen to family stories. HMS alumni who are themselves children of HMS alumni tell us what is was like to grow up with a doctor at the breakfast table. An alumnus recalls moments in his early life when the efforts of his physician-parents straddled the terrors of bigotry and conflict to ensure their family's well-being and the well-being of history's most notable psychoanalyst. And an alumna describes how classic children's literature presents illness and death to its readers, young and old.

Lifelong bonds—with spouses, siblings, children, friends—are shaped, tended, and nourished by advice. Take, for example, the professional counsel delivered by John Collins Warren to his son J. Mason Warren (Class of 1832), as the younger sailed to Paris to study medicine. "Observe operations," wrote the elder Warren, "Get as near as possible. Anticipate the steps." And then there was his cautionary advice on social bearing: "Be on your guard against wine. No champagne. Take claret." As a parent, and a physician, I can only wonder which, if either, J. Mason followed.



Jeffrey S. Flier
Dean of the Faculty of Medicine
Harvard University

HarvardMedicine

Editor
Ann Marie Menting

Design Director
Paul DiMattia

Assistant Editor
Susan Karcz

Contributing Writers
Angela Alberti, Tenley Albright, M.R.F. Buckley, David Cameron, Elizabeth Cooney, Katie DuBoff, Stephanie Dutchen, Elissa Ely, Lester Grinspoon, Kevin Hill, Perri Klass, Sue McGreevey, Jake Miller, Peter Schur

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Phone: 617-432-7878 • **Fax:** 617-432-0446
Email: harvardmedicine@hms.harvard.edu
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JOHN SOARES

Letters to the Editor

CHART NOTES FROM OUR READERS

Dr. Joe

Patient care, clinical sciences, and bedside medical integrity might suffer under absurd mandates, but my father never let those things dull his love for the profession.

KATHERINE MURRAY-LEISURE '78
PLYMOUTH, MASSACHUSETTS

Pitch Perfect

In the Summer 2011 issue of *Harvard Medicine*, Joseph E. Murray '43B, reflected on the achievements of the Brigham kidney transplant program and how its investigators, beginning in 1953, opened up the field of viable human organ transplantation. Gertrude Elion and George Hitchings, who developed early immunosuppressive drugs that would ultimately be used to prevent organ rejection, were awarded the Nobel Prize in Physiology or Medicine in 1988. E. Donnall Thomas '46 developed bone marrow and stem cell transplantation, and, with my father, was corecipient of the 1990 Nobel Prize in Physiology or Medicine.

In June, my family and I were honored to attend an excellent Alumni Week faculty symposium on transplantation and craniofacial science that was dedicated to Joseph Murray's memory. Our sincere thanks to all who were responsible for that symposium: the HMS Alumni Association office, Brigham and Women's Hospital, and the dedicated professionals in plastic, craniofacial, and transplant surgery who presented at the symposium. My family and I, especially my mother, appreciated the kind tributes to Dad, who died just the previous November. We felt Dad's presence; we knew how much pleasure and joy he would have felt on this special occasion.

My father was full of vigor when I sat next to him for midday Thanksgiving dinner in Scituate on November 22, 2012. That evening at home in Wellesley, he watched the Patriots win their game against the New York Jets. He turned off the television, then suffered a cerebral hemorrhage, followed by a peaceful death four days later at (where else?) his second home, Brigham and Women's. He was surrounded by family, friends, and colleagues. He passed just a month after the death of his Nobel Prize corecipient.

Medicine can be a demanding profession. Patient care, clinical sciences, and bedside medical integrity might suffer under absurd mandates, but my father never let those things dull his love for the profession. He was ever the optimist. I can still hear him in the shower singing "What a Wonderful World":

I hear babies cry.
I watch them grow.
They'll learn much more,
Than I'll ever know.
And I think to myself,
What a wonderful world.

KATHERINE MURRAY-LEISURE '78
PLYMOUTH, MASSACHUSETTS

Stress Test

I enjoyed the "Sequelae" article in the Summer 2013 issue of *Harvard Medicine*. Despite having seen and treated many trauma cases during my long life in surgery, I never experienced a true mass casualty event even when I was running the emergency room at Massachusetts General Hospital. The same was true during my time in the Army; trauma cases occurred one or two at a time. I hope I never have to experience anything like what went on in Boston that day. It certainly must have been a test of character for the doctors involved.

QUENTIN STILES '55
PALOS VERDES ESTATE, CALIFORNIA

Apology Department

The Summer 2013 issue of *Harvard Medicine* included a letter titled "About Face" in which we mentioned the post-World War II closing of the Harvard Dental School. What we failed to then mention was that the school immediately reopened as the Harvard School of Dental Medicine and remains today a thriving academic research and education institution. We regret this oversight and extend an apology to our readers.

THE EDITORS OF *HARVARD MEDICINE*

Harvard Medicine *welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.*

TOMORROW TODAY

Class of 2017 gains white coats—and a glimpse of medicine's future

THE WORLD IN WHICH Harvard Medical School's newest students will pursue medical careers may be transformed in ways that are unimaginable today, but in his welcoming remarks at the traditional White Coat ceremony in late August, Jeffrey S. Flier, HMS dean, assured members of the School's Class of 2017 that they will be well equipped to shape the future of medicine.

"Medical science and medical practice are undergoing profound changes," Flier told the medical, dental, and doctoral students who gathered for the ceremony, "and these will continue to accelerate through your training years. This is a time when physicians and scientists, including our newest ones, will be called upon to demonstrate leadership if society is to tackle some of its toughest problems. I'm confident you are all up to the challenge."

While Flier and other speakers encouraged the students to embrace—and influence—the coming changes, Jules Dienstag, the Carl W. Walker Professor of Medicine and dean for medical education at HMS, provided perspective with a history lesson. Dienstag traced a time line of the School, from the days when lectures were delivered in Greek, Latin, and Hebrew to anyone who could pay a fee, through today, when the students sitting before him represented less than 4 percent of the 5,779 applicants seeking admission to the School.

Just as the medical school occupied several locations in Boston and Cambridge before settling into the marble buildings that now frame the Quad, its philosophy of medical education has also evolved, Dienstag said. He invited students to participate in the new pedagogic models being developed to emphasize team-based learning and to help provide leadership in medical education for generations to come. Students entering HMS this fall will be part of the first class to have access to a new clinical skills center.

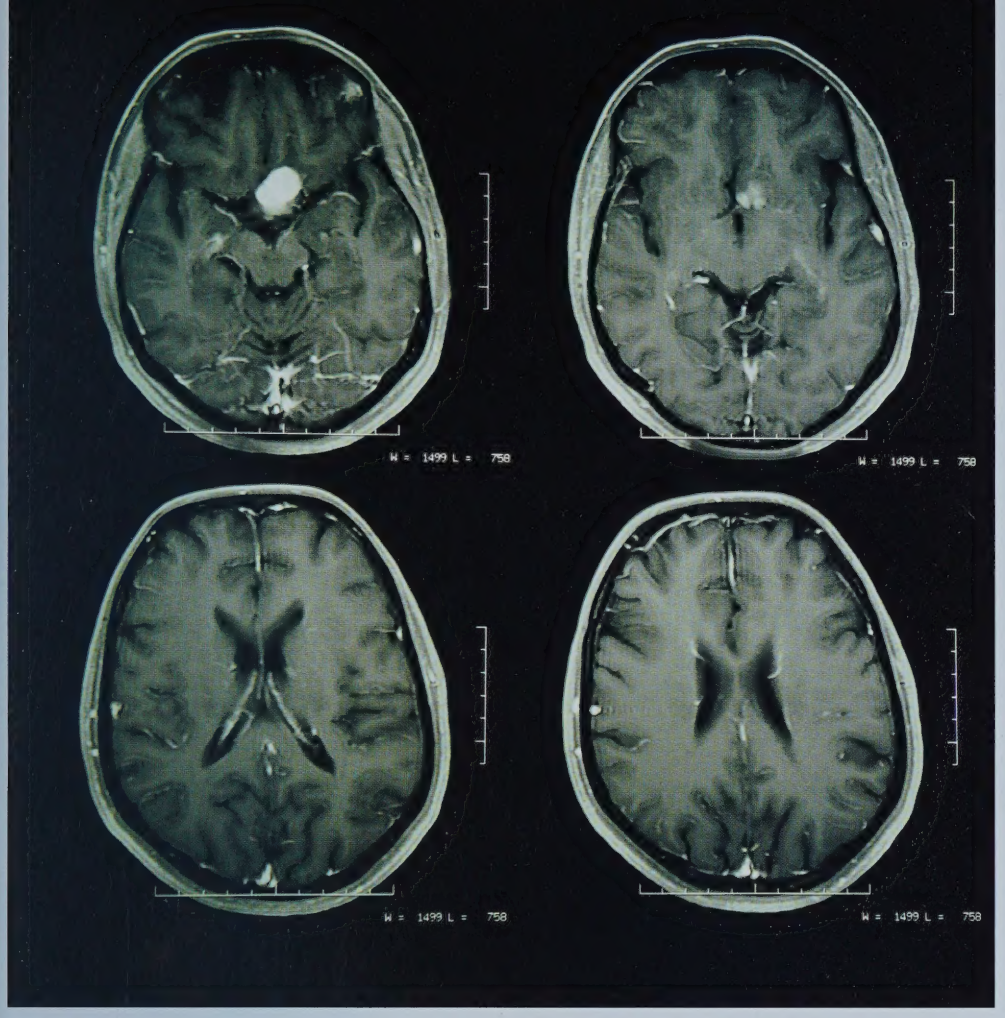
"We are very excited about who you will become," Dienstag said. "We know you have already been leaders before coming here. We have high expectations of you."

Flier underscored the need for new solutions to pressing problems in medicine, despite the explosion of knowledge in such medically relevant fields as regenerative biology, genomics, neuroscience, and systems biology.

Before heading to Brigham and Women's Hospital for the patient clinic, the students met in their societies to put on their white coats, an enduring tradition amid a changing world.

"Donning a white coat signifies a remarkable transition in your lives," Dienstag said in parting. "Wearing a white coat—a healer's cloak—bestows a mantle of privilege into the life of a patient." —*Elizabeth Cooney*

STEVE LIPOFSKY



A Cut Above

Neurosurgery achieves department status

RECOGNIZING NEUROSURGERY as a discipline distinct from general surgery, Harvard Medical School has established a Department of Neurosurgery as an academic department. The decision became effective October 1.

In a letter to the HMS community addressing the change, Jeffrey S. Flier, HMS dean, wrote, "It is important to note that an HMS graduate, Harvey Cushing, founded the field of neurosurgery a century ago while he was at the Peter Bent Brigham Hospital," now Brigham and Women's Hospital. Cushing was a member of the HMS Class of 1895.

The change in status to an appointing academic department was championed by the chiefs of neurosurgery at four of the School's affiliated hospitals. Three of the affiliates—Boston Children's Hospital, Brigham and Women's, and Massachusetts General Hospital—had previously housed hospital-based departments of neurosurgery, while Beth Israel Deaconess Medical Center had organized neurosurgery as a division of its Department of Surgery. These entities have been managing HMS faculty appointments for neurosurgeons and neuroscientists through their departments of surgery.

The new academic department will be governed by an executive committee led by Robert Martuza '73, the William and Elizabeth Sweet Professor of Neuroscience at HMS and chief of Mass General's Department of Neurosurgery. Martuza will serve a three-year term as the chair of the committee.

According to Nancy Tarbell, the C.C. Wang Professor of Radiation Oncology and HMS dean for academic and clinical affairs, this change brings potential benefits to the new department, including more direct oversight of faculty promotions; increased capability to recruit faculty; and comparability with peer institutions.

The decision to develop neurosurgery into an academic department was driven in part by the knowledge that, as a discipline, neurosurgery is recognized as a specialty distinct from general surgery in terms of training programs, fellowships, and specialty boards.

—Elizabeth Cooney

Renewed Interest

Harvard Catalyst will continue novel programs, initiatives

THE NATIONAL CENTER for Advancing Translational Sciences (NCATS) awarded a second five-year grant to the Harvard Catalyst, the Harvard Clinical and Translational Science Center. The grant is one of 15 clinical and translational science awards announced by NCATS in October. A total of $79 million in awards to these centers will support their work during the first year of funding.

Jeffrey S. Flier, HMS dean, congratulated program director Lee Nadler '73, HMS Virginia and D.K. Ludwig Professor of Medicine at HMS, and the many researchers, staff, and institutions involved in Catalyst's work, saying "The grant will allow us to continue to break new ground in clinical and translational research at Harvard and beyond. When we came together in 2008 to present our first application, we outlined a portfolio of bold, novel initiatives. Together, we have made significant progress. Now we will have the opportunity to advance these innovative programs and initiatives."

New Kids on the Quad

MEMBERS OF THE CLASS of 2017 have arrived, moved in, and begun their first year of medical training. The class is made up of 167 students, 54 percent of whom are women. Students hail from 72 colleges and universities located throughout 32 U.S. states, and from 8 other countries: Canada, China, Colombia, Mexico, Nigeria, Singapore, Vietnam, and Zimbabwe. The class roster includes students of Asian Indian, Cambodian, Chinese, Indonesian, Japanese, Korean, Nepalese, Pakistani, Taiwanese, Thai, and Vietnamese origin (28 percent); and minorities underrepresented in medicine (19 percent), a category that includes students who self-identify as black or African American, Hispanic other, Mexican American, Native American, and Puerto Rican.

Home Improvement

Renovation brings welcome changes to Tosteson Medical Education Center

IN MANY WAYS, the stately white marble buildings around the HMS quadrangle appear largely unchanged from when they were first erected in 1906. But visitors can now walk into one of them—the Tosteson Medical Education Center—and be transported into the 21st century.

The new Clinical Skills Center has materialized in a ground floor wing of the TMEC building, its gleaming halls stretching beyond etched glass doors emblazoned with the lion rampant from the HMS shield. The transformation began in February 2012, with the selection of the space; a committee approved plans in a mere six months, and construction on the $5 million facility began in February 2013.

"This new center will go a long way to advancing the educational experience of all our students," says Jules Dienstag, the Carl W. Walter Professor of Medicine and HMS dean for medical education. "It's the result of a tremendous collaborative effort and a credit to everyone who worked so diligently to make it a reality."

"We didn't want it to look too clinical," adds Jane Neill, the HMS associate dean for medical education planning and administration. "We worked with the architects to make it flow, given the constraints of the building." Neill was a driving force behind the new 7,500-square-foot facility. The center will be used for both teaching and assessing clinical communication and physical exam skills, and it will be the site in which students take their Objective Structured Clinical Exams. Faculty will also use the center to develop clinical teaching skills.

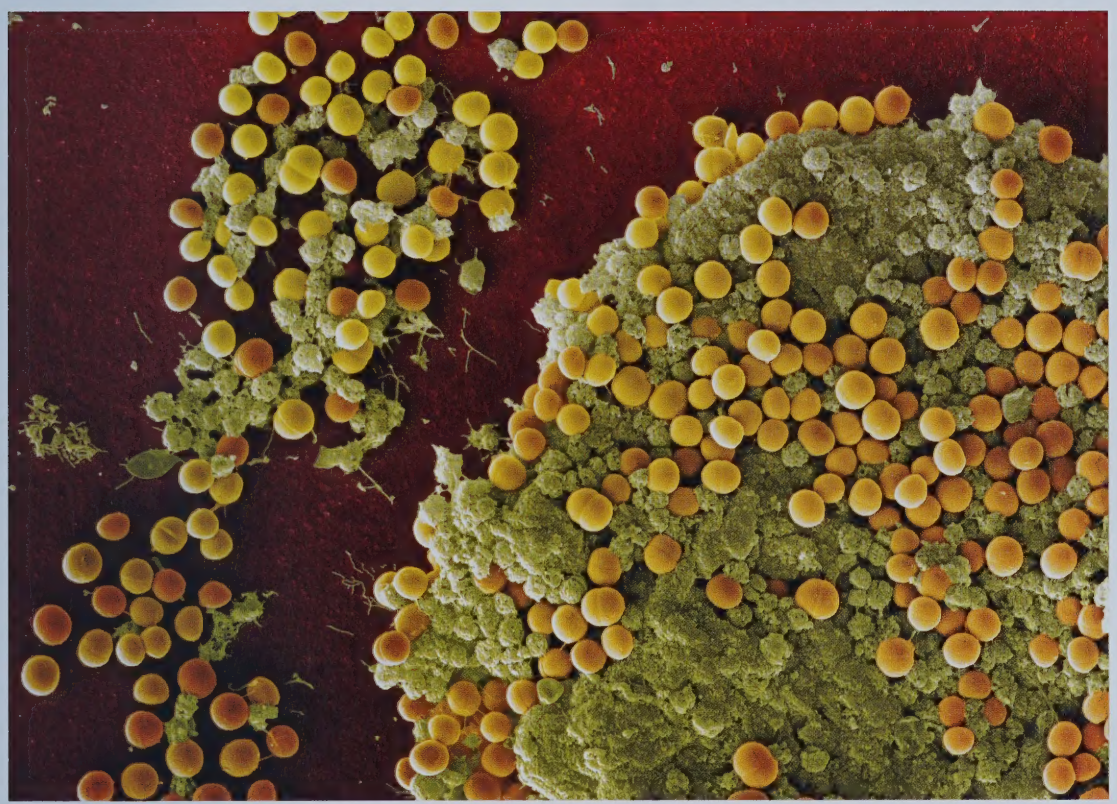
The space features 18 clinical exam rooms, including 10 with retractable walls, and a central room housing monitors and controls for 47 cameras used for observation and videotaping during exams and classes. Wireless simulation mannequins are stacked neatly in closets near exam rooms; students can check patients' records at computer-equipped kiosks nearby.

"One of the wonderful things about this space is that we've tried to be respectful of the history and the historical events that have occurred in this building," says Neill, who points out that along with all the technology that has been incorporated into the center's design, the halls are also graced with artwork, photographs, and medical objects on loan from the Center for the History of Medicine at the Francis A. Countway Library of Medicine.

"This renovation is a terrific example of what you can do with an old building," says Rick Shea, HMS associate dean for campus planning and facilities. "It shows that it is possible to breathe new spirit into existing, historic structures, and to extend their usefulness into a new century."

—M.R.F. Buckley

JOHN SOARES



SCIENCE PHOTO LIBRARY

REVEALING THE SOURCE

Virulent bacteria found to cause infection pain

THE PAIN OF invasive skin infections, such as those caused by methicillin-resistant *Staphylococcus aureus*, appears to be induced by the invading bacteria themselves, and not by the body's immune response, report HMS scientists at Boston Children's Hospital. What's more, their research demonstrates that once the pain neurons "sense" the bacteria, they suppress the immune system, potentially helping the bacteria become more virulent.

The study, which used a mouse model, could change the way doctors think about a variety of invasive painful infections, such as meningitis, necrotizing fasciitis, urinary tract infections, dental caries, and intestinal infections. The research was published in the September 5 issue of *Nature*.

"If we could block pain in infected tissues and also block what pain neurons do to the immune system, it could help us treat bacterial infections better," says Isaac Chiu, the study's first author and a neuroimmunologist in the laboratory of Clifford Woolf, an HMS professor of neurology at Boston Children's F.M. Kirby Neurobiology Program.

The research was spurred when the scientists observed the interaction of cultured sensory neurons and immune cells during an infection. "Surprisingly, the neurons responded immediately to the bacteria," says Chiu. That observation led the researchers to move to a live model of skin infection, the first, they think, ever used to study pain.

In the study, Chiu and colleagues examined pain, tissue swelling, immune cell numbers, and the number of live bacteria in mice with staphylococcal skin infections. They found that pain levels tracked closely with the number of live bacteria and peaked well before tissue swelling did, indicating that the bacteria, not a local inflammatory response, were the cause of the pain. The team also documented communication between bacteria, pain neurons, and cells from the immune system.

The research showed that *S. aureus* secretes two kinds of compounds that communicate with sensory neurons and help induce pain. These *N*-formyl peptides, which can be detected by receptors on pain neurons, and pore-forming toxins, which are secreted by virulent bacteria, dock on the sensory nerve terminals and create pores that let ions enter the nerve cells, triggering them to fire off pain messages.

The finding that pain neurons, once activated by bacteria, suppress the immune system was equally unexpected. Why would activated pain neurons try to weaken the immune response to infection? Chiu speculates that the neurons are functioning to protect tissues from further damage caused by an inflammatory immune response—a protective mechanism that bacteria might be exploiting to their advantage.

Move It, Move It

Exercise may rival drugs in reducing the risk of death in common conditions

PHYSICAL ACTIVITY has powerful life-saving effects for people with serious chronic conditions, according to a study by scientists at Harvard Pilgrim Health Care Institute. In research published online October 1 in *BMJ*, a team of investigators led by Huseyin Naci, an HMS visiting fellow in population medicine at the Institute and a graduate student at the London School of Economics, showed that exercise is potentially as effective as many drug interventions for patients with cardiovascular disease and other chronic conditions. The researchers say the study is the first to assess the comparative benefits of drugs and exercise for reducing mortality in a range of illnesses.

"We were surprised to find exercise showed such powerful life-saving effects for people with serious chronic conditions," says Naci, "and that so little is known about the potential benefits of physical activity in so many other illnesses."

Four conditions in which the effects of exercise on reducing mortality had been studied were prevention of severe illness in patients with coronary heart disease, rehabilitation from stroke, treatment of heart failure, and prevention of diabetes.

For the study, the researchers analyzed the results of 305 randomized controlled trials involving 339,274 individuals and found no statistically detectable differences between exercise and drug interventions for secondary prevention of heart disease and prevention of diabetes. Among stroke patients, exercise was more effective than drug treatment, while in congestive heart failure, diuretic drugs were more effective than all other therapies, including exercise.

The authors point out that the amount of trial evidence on the mortality benefits of exercise is considerably smaller than that on the benefits of drugs, and that this may have had an impact on their results. Of the nearly 340,000 cases analyzed, fewer than 15,000 included exercise-based interventions.

In the United States, 80 percent of people 18 and older failed to meet the guidelines for aerobic and muscle-strengthening physical activity in 2011, according to the Centers for Disease Control and Prevention. —*Jake Miller*

In the Thick of It

Reducing activity of a mutant protein may prevent hypertrophic cardiomyopathy

HYPERTROPHIC CARDIOMYOPATHY (HCM), a disease in which the heart is weakened by the thickening of cardiac muscle, abides in an estimated 1 in 500 people in the United States. Although many of these individuals never develop symptoms, for others the disease can be severe or fatal. HCM is, in fact, the leading cause of sudden heart-related death in athletes and other people under the age of 30 in this country.

According to a study by HMS researchers, there may be a gene-based path to preventing this disease. In the research team's paper in the October 3 issue of *Science*, senior author Christine Seidman, the Thomas W. Smith Professor of Medicine, an HMS professor of genetics at Brigham and Women's Hospital, and a Howard Hughes Medical Investigator, reports that, in a mouse model, reducing the production of a mutant protein prevented HCM from developing for several months.

More than 1,000 different mutations that can cause HCM have been identified across about 10 genes that make heart muscle proteins. People with the disease have one "good" copy and one "bad" copy of one of those genes.

Studying one of the mutations that causes a particularly severe form of the disease in humans, Seidman, together with her colleague Jonathan Seidman, the Henrietta B. and Frederick H. Bugher Foundation Professor of Genetics at HMS, and others, targeted the analogous mutant gene in mice while leaving the normal gene alone.

Using an RNA interference (RNAi) tool they designed, the scientists homed in on the single HCM-causing mutation and stopped it from making its harmful protein. They then compared the results to those from two untreated groups of mice: one with the same HCM mutation and one without.

Suppressing the mutated gene reduced production of the deleterious protein by about 28 percent, enough to prevent development of HCM manifestations—including ventricular wall overgrowth, cell disorganization, and fibrosis—for about six months, or one-quarter of a mouse's lifespan.

"For all intents and purposes, the heart looked normal," says Christine Seidman. "Wonderfully, boringly normal."

The treatment successfully targeted heart cells in the mice without affecting other organs. Although it did not reverse any existing HCM damage, Jonathan Seidman notes that having the ability to limit progressive symptoms would be a significant step forward.

—*Stephanie Dutchen*

REPAIR KIT

Researchers identify novel approach to enhancing tissue growth

BECAUSE MOST HUMAN TISSUES do not regenerate spontaneously, advances in tissue repair and organ regeneration could benefit many patients confronting a variety of medical conditions.

One such advance—a new approach to enhancing normal tissue growth—has been announced by a team of investigators from Beth Israel Deaconess Medical Center and Dana-Farber/Boston Children's Cancer and Blood Disorders Center. The findings, published in the August 13 issue of the *Proceedings of the National Academy of Sciences*, could have widespread therapeutic applications.

Although tissue regeneration is a process that is not fully understood, previous research has shown that endothelial cells lining the insides of small blood vessels play a key role in tissue growth. Those same endothelial cells also generate chemical messengers called epoxyeicosatrienoic acids (EETs), which stimulate blood vessel formation in response to tissue injury.

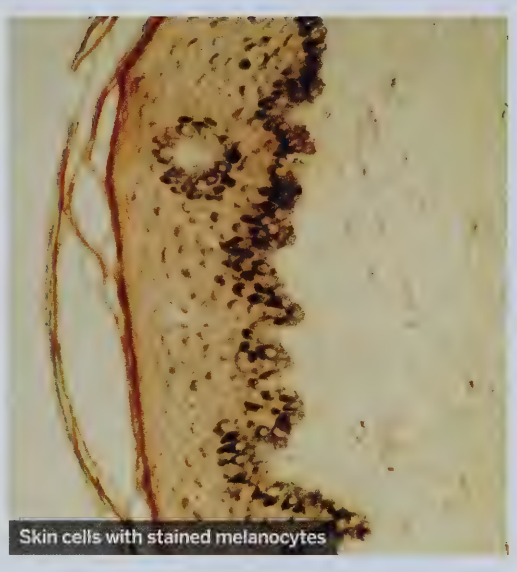
Together with his research colleagues, Dipak Panigrahy, an HMS instructor in pathology, an investigator in Beth Israel Deaconess's Center for Vascular Biology Research, and the paper's first author, set out to determine how EETs might participate in organ and tissue regeneration. To do this, they created seven mouse models, each exemplifying a different system: liver, kidney, and lung regeneration; wound healing; corneal vascularization; retinal vascularization; and angiogenesis.

The team used genetic and pharmacologic tools to manipulate EET levels in the animal models, then assessed the role that EETs played in accelerating tissue growth. They found that administering synthetic EETs spurred tissue growth in the research models, while the lowering of EET levels, either by manipulating genes or administering drugs, delayed tissue regeneration.

The team also showed that proteins called soluble epoxide hydrolase (sEH) inhibitors promoted liver and lung regeneration. These proteins are the main metabolizing enzymes of EET and are known to elevate EET levels.

According to Panigrahy, the findings provide a rationale for evaluating sEH inhibitors as novel therapeutics for such conditions as hepatic insufficiency after liver damage, and for diseases characterized by immature lung development, such as bronchopulmonary dysplasia. He also notes that the use of topical sEH inhibitors might help accelerate the healing of skin wounds.

Blood vessel endothelium



Skin cells with stained melanocytes

Heads Up, Red

Mutation for red hair also triggers a cancer-promoting pathway

MELANIN, the pigment that determines hair color and skin tone, is influenced by the *melanocortin-1* (*MC1R*) gene receptor. A certain mutation in *MC1R* results in the familiar physical characteristics of redheads.

Now HMS researchers have discovered that *MC1R-RHC*, the mutation responsible for the red-hair phenotype, also triggers an important cancer-promoting pathway. The findings, reported in the August 22 issue of *Molecular Cell*, help explain the molecular mechanisms that underlie redheads' well-known risk of developing melanoma and may provide new insights for preventing and treating this dangerous type of skin cancer.

Melanoma is the least common but the most lethal of skin cancers. Accounting for 75 percent of all skin-cancer deaths, it originates in pigment-producing skin cells called melanocytes. Two types of UV radiation—UVA and UVB—can mutate DNA in these skin cells and lead to melanoma.

"In this current study, we have demonstrated that the mutation *MC1R-RHC* promotes the PI3K/Akt signaling pathway when a red-haired individual is exposed to UV radiation," says co-senior author Wenyi Wei, an HMS associate professor of pathology at Beth Israel Deaconess Medical Center. PI3K/Akt is a well-known cancer-promoting pathway implicated in breast, ovarian, and lung cancers.

The team also found that in the *MC1R-RHC* pigment cells, elevated PI3K/Akt activity boosted cell proliferation and synchronized with another well-known cancer mutation in the *BRAF* gene to accelerate cancer development.

Interior Shots

Neural abnormalities seen in schizophrenia

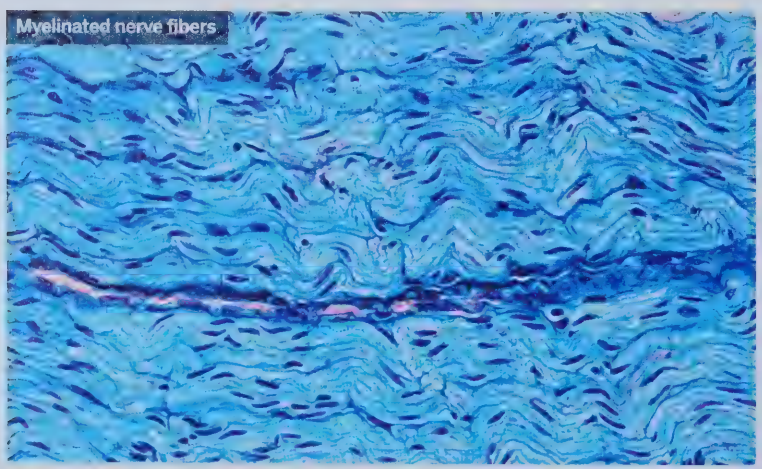
IMAGING TECHNIQUES used by HMS researchers at McLean Hospital may have pulled back a bit further the curtain that masks our understanding of the brain activity of people diagnosed with schizophrenia. In work published in the September 15 issue of *Biological Psychiatry*, senior author Dost Öngür, an HMS associate professor of psychiatry at McLean, and colleagues describe myelin and axon abnormalities they found when using magnetic resonance imaging to peer into the brains of individuals with the disorder.

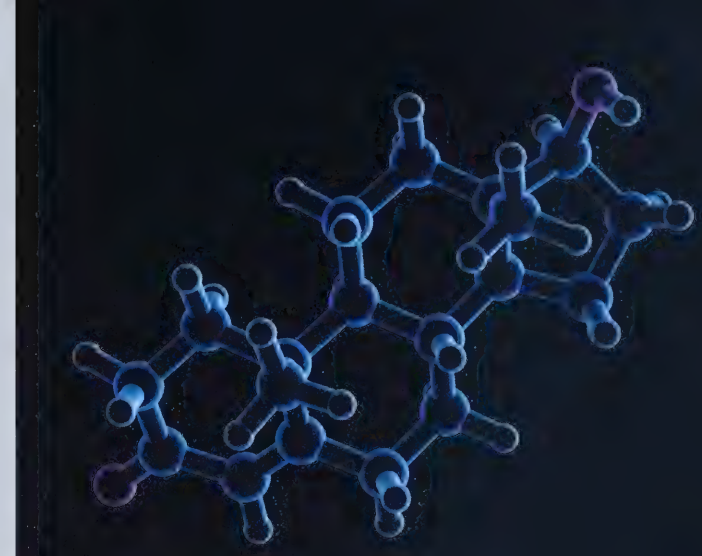
For their study, the researchers enrolled 22 healthy control individuals from the community and 23 individuals diagnosed with schizophrenia who were participating in the hospital's clinical services. The study's design called for each group to undergo two types of imaging: magnetic resonance imaging, to measure the levels of particular chemicals in the brain, and magnetization transfer imaging, to detect changes in the degree of myelination in the neural white matter. Myelin, which wraps around nerve cells, helps the cells transmit signals from one part of the brain to another.

Scientists have long known that the brain in schizophrenia has abnormalities in connections between brain regions, and that imaging has suggested that the abnormalities can be traced to the white matter. But until the present study, researchers have not had the tools to pinpoint whether the abnormalities occurred in the nerve cell extensions known as axons or in the myelin sheath around the axons, or both.

When comparing images from the control group with those from the test group, the research team found abnormalities in both myelin and axons in the brains of people diagnosed with schizophrenia: a reduced myelination of white-matter pathways and an increased diffusion of *N*-acetylaspartate, an amino acid found in neurons. *N*-acetylaspartate is thought to indicate nerve cell activity.

The findings, say the authors, suggest that the speeds of the signals traveling along myelinated fibers are abnormal in schizophrenia, possibly leading to information processing difficulties and cognitive deficits.





Male Carriers

Drops in estrogen contribute to some signs of age-associated changes in men

JUST AS THE SYMPTOMS of menopause in women are attributed to a sharp drop in estrogen production, the signs of aging often seen in men—changes in body composition, energy, strength, and sexual function—are usually attributed to a less drastic decrease in testosterone production that typically occurs in the middle years.

HMS researchers at Massachusetts General Hospital have found that insufficient estrogen could be at least partially responsible for some of these changes in men. The study appeared in the September 12 issue of the *New England Journal of Medicine*.

Traditionally, a diagnosis of male hypogonadism—a drop in reproductive hormone levels great enough to cause physical symptoms—has been based solely on a measure of blood testosterone levels. But there has been little understanding of how much testosterone is needed to support certain physical functions.

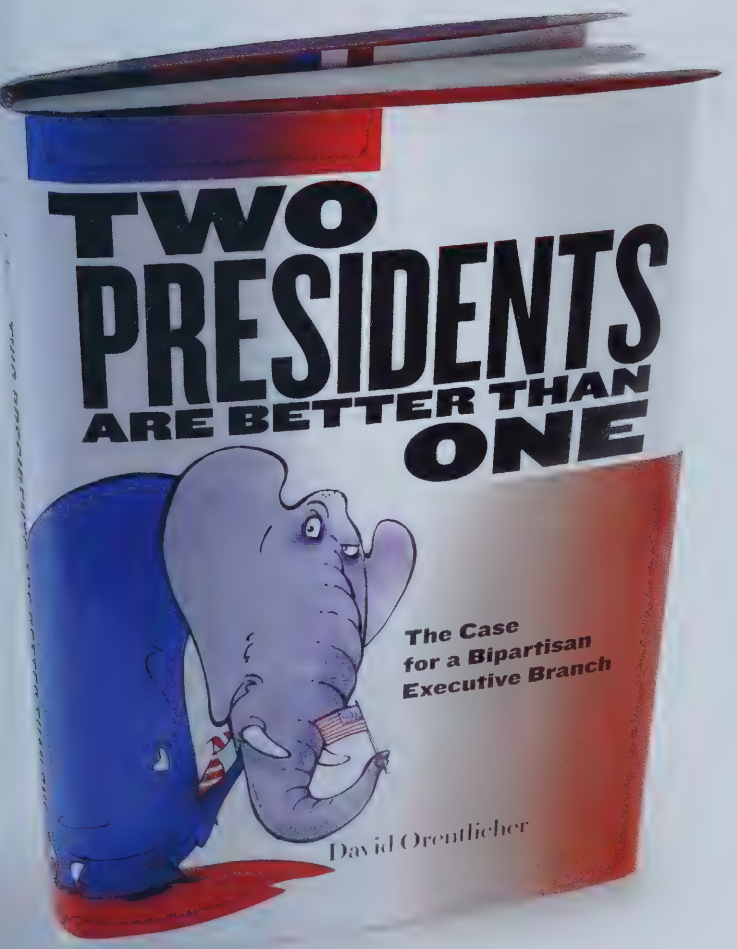
A small portion of the testosterone that men make is normally converted into estrogen by an enzyme called aromatase. The higher the testosterone level in a healthy man, the more is converted into estrogen. Since any drop in testosterone means that there is less to be converted into estrogen, men with low testosterone also have low estrogen levels, making it unclear which hormone supports which functions. The Mass General team set out to determine the levels of hormone deficiency at which symptoms begin to occur in men and whether those changes are attributable to decreased levels of testosterone, estrogen, or both.

The study enrolled two groups of men, ages 20 to 50, with normal reproductive function. All participants were treated with a drug that suppresses normal production of all reproductive hormones.

Men in one group were randomly assigned to receive daily doses of testosterone gel at one of four dosage levels or a placebo gel for 16 weeks, while men in a second group received the same testosterone doses plus an aromatase inhibitor that suppressed the conversion of testosterone into estrogen.

Overall, the results imply that testosterone levels regulate lean body mass and muscle size and strength, while estrogen levels regulate fat accumulation. Sexual function—both desire and erectile function—is regulated by both hormones.

—Sue McGreevey



PARTY MIXER

Two Presidents Are Better Than One: The Case for a Bipartisan Executive Branch
by David Orentlicher '81
(NEW YORK UNIVERSITY PRESS, 2013)

reviewed by Elissa Ely

IT'S BEEN SEVERAL INCARNATIONS (if ever) since I had intelligent thoughts about the Federalist Papers and the Founding Fathers. One gets waylaid by the starker concerns of the moment.

But I do recall one thing the Constitution put in place: a single president.

So it was intriguing to notice a donkey and an elephant, wearing wing tip shoes and sharing a single suit, on the cover of *Two Presidents Are Better Than One: The Case for a Bipartisan Executive Branch*, by David Orentlicher '81. What better reason to leave prior authorizations and consent forms for a while and ponder the presidency?

Let us dig in. Orentlicher argues (and he can do it—he's a law professor as well as a physician) that in the years since the framers conceived the position, presidential power has undergone an unanticipated and mangled expansion. Back in 1787, our forefathers envisioned "a president with limited authority, who would serve as a coequal with Congress [because] power should be contained by dividing it and requiring it to be shared."

Then human nature intervened. It generally does. The system "worked reasonably well for the first 150 years, but since the 1930s it has collapsed." What evolved instead of coequality was an "imperial presidency," driven every four to eight years by one man's perspective and ambitions. Presidents no longer executed domestic and foreign policies created by Congressional majority: Instead, like monarchs, they created policy themselves. And human nature being what it is, response from the Congressional party out of control (and luck) deteriorated into virulent partisanship.

Think of it: personal legacy, profit, aggression—all those unsightly motivations (to which, Orentlicher points out, doctors and husbands are also susceptible). Imperial presidencies led to Watergate, enhanced interrogations, and military actions without authorization.

But there is an alternative: a coalition presidency. It requires a constitutional amendment, and, given that it would have a pair of heads, might look like an alien at first glance. But in a coalition presidency, there are no shenanigans for personal gain. Nor is there partisan gridlock from the minority, since there is no party dominance. Instead, there are those two flag-waving beasts emerging from one suit, working collaboratively on all decisions from State of the Union texts to judicial nominations, supported by a Congress with unembittered bipartisan influence.

The rest of Orentlicher's book is defense. He fends off our accusation that he's dreaming by citing game theorists to explain how two presidents wouldn't lock horns. He uses examples of other countries where executive power is already shared. And he even throws in a statistic to cherish from *Who Wants to Be a Millionaire*: use your audience lifeline; it will help you 91 percent of the time.

There are historical examples—the Roman Republic was headed by two consuls—and fantasies of how U.S. history might have been changed: a Nixon–Kennedy presidency could have prevented the Bay of Pigs invasion; an Obama–McCain presidency could have reconfigured the economic stimulus package successfully. With the internal check of a presidential partnership, there might even be an end to term limits, allowing time to chip blocks of policy into sculpture rather than bludgeoned stone.

No detail is too small to consider, and Orentlicher considers them all. Two presidents, for instance, would have to live in shared personal space in the White House. This would require some of the "guest quarters . . . to be converted to presidential space." No problem. In his enthusiasm, he has all but taken measurements.

This intelligent and revolutionary book saved me from a long afternoon on the phone with pharmacies. But that's nothing, considering it might save the country, too.

Elissa Ely '87 is a psychiatrist at the Massachusetts Mental Health Center.

SECOND OPINIONS

EXAMINING THE USE OF MEDICAL MARIJUANA

"What should physicians consider before recommending the use of medical marijuana to their patients?"

Perspectives from Lester Grinspoon and Kevin P. Hill

Lester Grinspoon:

In 1967, out of concern over the rapidly growing use of marijuana, then considered a dangerous drug, I began to review the scientific and medical literature, looking for a reasonably objective summary of the data supporting the drug's prohibition. To my surprise, I found no credible scientific basis for its prohibition.

The assertion that marijuana is a toxic drug is based on old and new myths. In fact, one of the exceptional features of this drug is its remarkably limited toxicity. Compared to aspirin, which people are free to purchase and use without the advice of or a prescription from a physician, cannabis is much safer: There are well over 1,000 deaths annually from aspirin in the United States alone, whereas there has never been a death anywhere from marijuana. By the time cannabis regains its place in pharmacopoeias around the world, it will be regarded as one of the safest drugs in those compendiums. Moreover, I believe it will eventually be hailed as a "wonder drug," just as penicillin was in the 1940s.

It may not be surprising to learn, therefore, that marijuana's use as a medicine, legally or illegally, with or without the recommendation of a physician, is growing exponentially worldwide. In the United States, with the recent addition of Massachusetts, 20 states and the District of Columbia have established legislation that makes it possible for patients suffering from a variety of disorders to use the drug legally with a physician's recommendation.

Unfortunately, because each state arrogates to itself the right to define which conditions may be lawfully treated with cannabis, many patients with legitimate claims to the therapeutic usefulness of this plant must continue to use it illegally—and endure additional anxiety as a result. California and Colorado allow its legal use for the widest number of medical conditions. New Jersey is the most restrictive; I would guess that in that state only a small number of patients who would find marijuana to be as or more useful as other, invariably

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Lester Grinspoon

One of the exceptional features of this drug is its remarkably limited toxicity.

more toxic, conventional drugs are allowed legal access to it.

Perhaps because so many patients have discovered for themselves that marijuana is both relatively benign and remarkably useful, the consensus that cannabis is evil is being undermined. The only workable way of realizing the full potential of this remarkable substance, including its full medical potential, is to free it from the present dual set of regulations—those that control prescription drugs in general and the special criminal laws that control psychoactive substances. These mutually reinforcing laws establish a set of social categories that strangle its uniquely multifaceted potential. The only way out is to cut the knot by giving marijuana the same status as alcohol—legalizing it for adults for all uses and removing it entirely from the medical and criminal control systems.

Lester Grinspoon '55 is an HMS associate professor of psychiatry emeritus, and author of Marihuana Reconsidered, *and, with James B. Bakalar, of* Marijuana, the Forbidden Medicine.

Kevin P. Hill:

In November 2012, residents of the Commonwealth of Massachusetts voted overwhelmingly in favor of medical marijuana. Their sentiments echoed those of voters in the rest of the country; as of October 2013, 20 states and the District of Columbia had enacted medical marijuana laws. The genie is out of the bottle, and there is no turning back.

In 2008, Massachusetts decriminalized possession of less than one ounce of marijuana—an amount sufficient to roll 80 joints. The new medical marijuana regulations stipulate that those with medical marijuana cards can possess up to 10 ounces of marijuana as a 60-day supply, an incredibly large amount. And it is important to note that marijuana is more potent than ever. If you recall marijuana from the sixties and seventies, today's marijuana is more than 10 times as strong.

It must also be noted that most people who use marijuana occasionally do not become addicted to it, but 9 percent of adults and 17 percent of young people who use it develop addiction problems. Marijuana is not a harmless drug; like alcohol, it is a substance that some can use without difficulty while others have problems that affect school, work, and relationships.

Medical marijuana has been available in Massachusetts since January 1, 2013. Patients may obtain a certification—not a prescription—from a doctor and that certification allows them to possess medical marijuana. Patients can get medical marijuana for "debilitating conditions," such as cancer, multiple sclerosis, or any other condition for which their physician sees fit to recommend it. This is another potential problem. While I can accept patients with such conditions using medical marijuana, my concern is that most people who receive recommendations will have conditions other than the ones specified in the laws.

Physicians are in a difficult position due to the demand for a treatment that is both federally illegal and lacking strong scientific evidence supporting its medical use.

Medical marijuana is a substance that some can use without difficulty, while others have problems that affect school, work, and relationships.

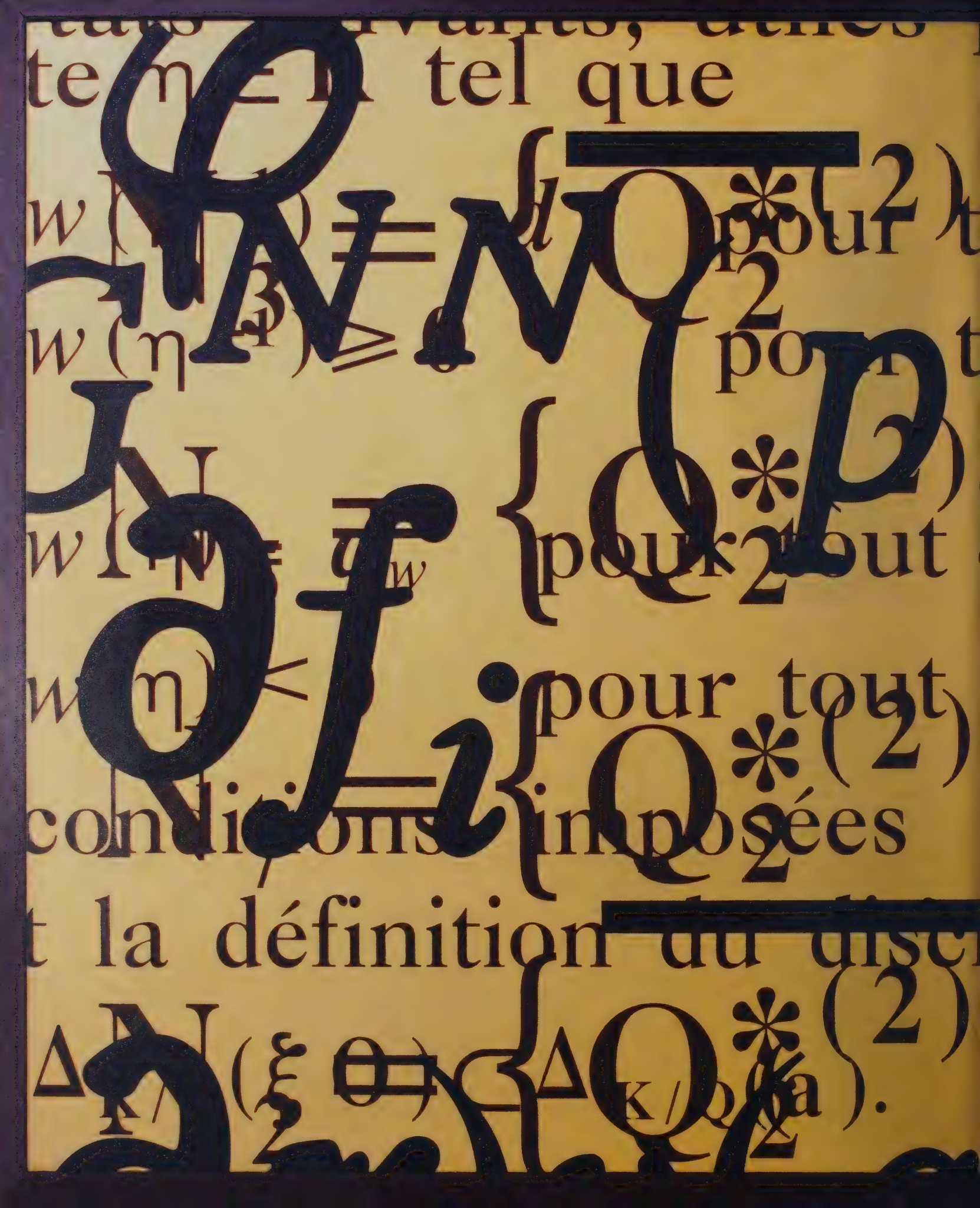

Kevin P. Hill

Marijuana and other cannabinoids have been studied as treatments for a large number of medical conditions without much luck. Cannabinoids have been found to be effective in treating nausea and vomiting associated with cancer chemotherapy, and poor appetite associated with certain illnesses. There are, however, FDA-approved cannabinoid medications (dronabinol and nabilone) for these problems, so it is difficult to explain the need for the marijuana plant as medicine.

Physicians must weigh the risks and potential benefits of medical marijuana on a case-by-case basis. Oncologists or neurologists treating patients for the debilitating illnesses specified in the medical marijuana regulations may wish to recommend it as a treatment, particularly if multiple medication trials have not produced relief. Many other physicians, including psychiatrists like me, will probably find that patients requesting medical marijuana have such illnesses as mood disorders or addiction that make them poor candidates for its use. So far, the non-FDA-approved status of marijuana—and the lack of support by any major medical organization—has made most physicians reluctant to recommend it to their patients.

Kevin P. Hill is an HMS assistant professor of psychiatry at McLean Hospital and director of the Substance Abuse Consultation Service in the hospital's Division of Alcohol and Drug Abuse.

The opinions presented are those of the contributors and do not necessarily reflect those of the President and Fellows of Harvard University or the publishers of Harvard Medicine *magazine.*



Infants are surrounded by clouds of language that shape their brains and their worlds

by Susan Karcz

A Way With Words

The stories of our own beginnings, whether tales of cultural origins or a retelling of a young child's first words, have an enduring appeal. ■ Such stories also hold significance. Accounts of a youngster's first words may become part of the foundation on which a family builds an identity. Twenty years later, a child's "gank you" rendition of "thank you" has become part of a family's lexicon, spoken when the parents wish to telegraph a cherished memory. ■ Variants of this story are told every day all over our world, as infants effortlessly acquire one or more languages. But how does this commonplace come to pass? ■ It is this question that researchers are attempting to answer when they investigate not only how infants acquire language, but also how they gain the many complementary skills they will need to live in their world.

ON Q: Even before birth, the brain of an infant responds to and explores the concepts of language, just as French artist Bernar Venet does visually in his mathematical saturation paintings, such as the work at left: *Gold Saturation with four Q* (2008, acrylic on canvas, 200 x 200 cm).

ARCHIVES BERNAR VENET, NEW YORK

TALKING SHOP: Determining how infants learn and become facile with language underpins research by Takao Hensch (clockwise), Karin Stromswold, and Claudio Toppelberg.

JOHN SOARES; JACOB FELDMAN (ABOVE, RIGHT)

A Human Condition

Babies are primed to learn language—any language—while still in the womb, and are born ready to continue the task. Takao Hensch, an HMS professor of neurology at Boston Children's Hospital, puts it this way, "All infants are born as citizens of the world, meaning that an infant born in Japan could just as easily acquire English as Japanese or any other language."

The newborn brain is highly plastic; that is, it can readily form new synaptic connections, the types of connections that are vital to processing the continuous streams of new information infants glean from what they hear, see, and touch. Research shows that in the early postnatal period, an infant's brain forms an abundance of neural connections, and then, over time and in response to environmental influences and experience, pares those connections that are not useful. In language development, this process of perceptual narrowing, says Hensch, allows the brain to rewire itself to better represent its native speech or language. Hensch, whose research focuses on how early life experience physically shapes the brain, adds that "the brain is simply doing what it is good at. It is retaining that which is important and removing that which is not."

Hensch's research into critical periods, windows of rich developmental opportunity in early life, has shown in animal models that optimal development requires stimulation while neural connections are maturing. In human infants, for example, this means that if family members talk directly to an infant during the first six months of her life, the baby's brain will more readily form the strong neural connections necessary for future language development. Without this kind of stimulation, an infant will still learn a language, but on a less-than-ideal foundation.

Critical periods occur when neural activity is tempered, a situation triggered by the action of inhibitory cells. As the brain matures, inhibitory neurotransmitters are released, slowing down the robust synaptic activity of the early postnatal period. In addition, imaging shows that critical periods occur at different times. Says Hensch, "depending on what aspect of language you're interested in, the activated region will be in a different part of the brain and at a different time in development when things are most plastic."

An example of how these critical periods manifest can be found in young children as they learn the components of language, says Karin Stromswold '91, a professor of psychology and cognitive science at Rutgers University. For anyone who has struggled to learn a second language as an adult, the speed with which young children learn language is breathtaking. As Stromswold explains, "there is reason to believe that children are actually already learning language prior to birth. The uterus is not a soundproof booth."

At birth, babies already know something about the phonology (sound system) of their language and can tell the difference between their mother's native language and a language that has a different rhythmic pattern. Before age one, most babies understand the meanings of a dozen or so words, and by two years of age, most children can say 200 or more words. Young toddlers also know a surprising amount about the morphology and syntax of their language. Although they often omit words and endings, saying things like "baby spill milk," and "kitty eating"—and three- and four-year-olds occasionally use the wrong forms of irregular nouns and verbs, saying, for example, "mouses" and "eated"—they nearly always say words in the correct order: They don't, for instance, say, "milk spill baby" or "eating kitty." Remarkably, by the time children start kindergarten, the vast majority of what they say is grammatical.

Stromswold's research on how prenatal and neonatal factors interact with genetic factors to influence linguistic and non-linguistic development suggests that the more formal aspects of language (syntax, morphology, and phonology) may have a stronger genetic component than, for example, vocabulary or discourse and pragmatics (the social aspects of language), each of which is more influenced by the postnatal environment.

Twice as Nice

Babies born into bilingual or multilingual families are as prepared for learning two or more languages as they are for learning one, and research has shown that they can distinguish between two languages before six months of age. The brains of babies who learn sign language accommodate the

visual, rather than auditory, inputs of sign by "repurposing" regions of the visual cortex to become language centers.

Neuroimaging has underscored how early learning of more than one language can change the brain. A study in which researchers compared the brain scans of adults who had acquired a second language after age 11 with like scans of adults who had grown up bilingual found activation differences in Broca's area, a region of the frontal lobe associated with language production. For adults who had grown up bilingual, the neurons in Broca's area, in response to speech, fired in a diffused pattern. For the adults who had acquired a second language as an adolescent, activation sites were discrete and separable.

Neural activation differences can also be seen in the brains of bilingual adults who code-switch; that is, deftly switch languages in response to social cues. Hensch notes that "bilingual adults use part of the basal ganglia system typically associated with motor control and sequencing patterns and movement—and you can see, on scans, when they code-switch. There is activation in a particular spot when they are switching from one language to another." This fluency can manifest in bilingual children by or before age three.

Studies in single-language twins reveal other aspects of language acquisition. Nearly all twins are born prematurely and at low birth weights, so, as Stromswold notes, "twins who are developing normally are, on average, two to three months delayed in language development relative to singletons, even when we correct for their prematurity. Twins are also two to three times as likely to be diagnosed with language impairments as singletons."

It has been assumed that twins' language lag is linked to their hearing less child-directed speech from their parents than single-born children do. Stromswold's research, however, suggests that much of twins' language delay results from their being more likely to experience perinatal hardships associated with being born prematurely and at low birth weights.

The Social Variable

Babies may come into the world ready to learn language, but as good as they are at doing this, they cannot accomplish it alone. Whether learning one language or three, babies need to engage with human speech to shape their newly forming neural connections.

According to Claudio Toppelberg, a child and adolescent psychiatric researcher and an HMS assistant professor of psychiatry at the Judge Baker Children's Center, children in the United States whose first language, or home language, is not English need active support to develop language skills. And U.S. public schools are not currently providing that support. Toppelberg says that his research in the Boston public schools found that dual-language children—the term dual-language is generally favored; the term bilingual suggests equal proficiency in two languages—learn English "at a pace that you almost never see in monolingual children." He adds that it is incorrect to conclude that young children have "room" for only one language. Although it takes years to master the formal language needed for learning, "there is no evidence that developing a first language undermines the learning of English as a second language." In fact, he says, even children with learning disabilities can successfully learn two languages.

Toppelberg considers "children's dual-language ability" a treasure that should be nourished. Current research, in fact, shows that the greater conscription of resources marshaled in learning and simultaneously managing multiple languages may lead to better executive functioning, impulse control, and problem solving.

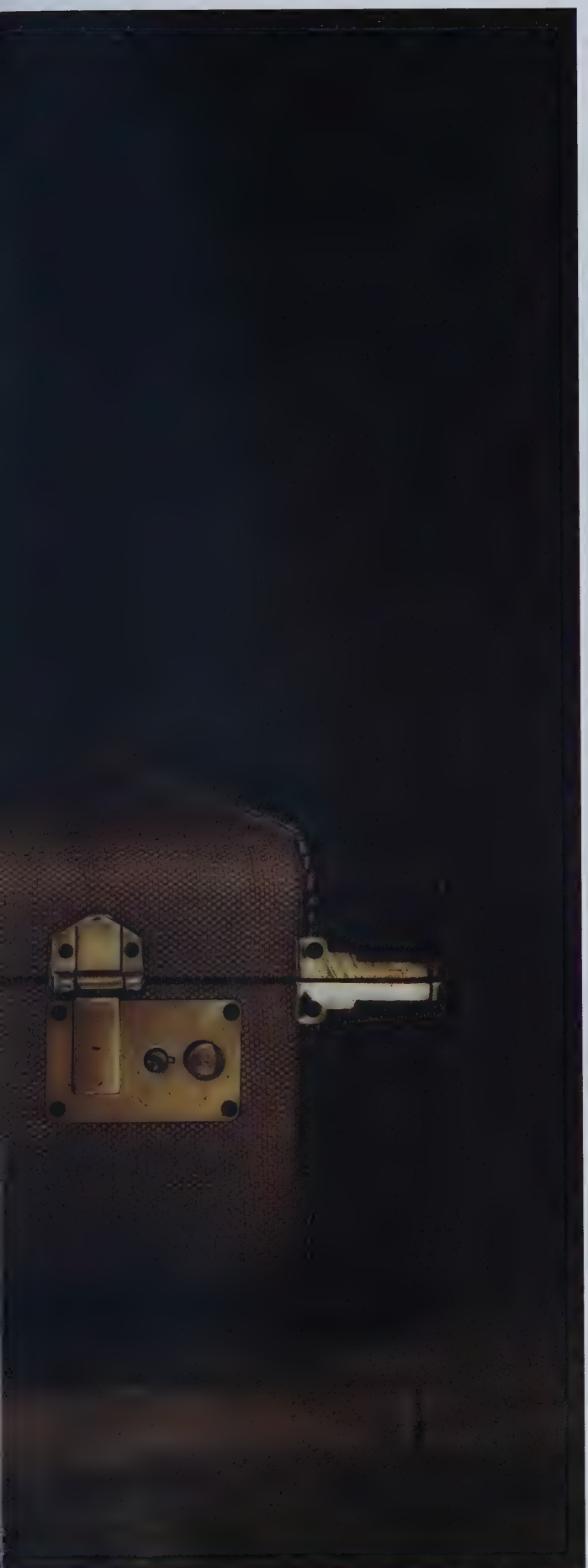
According to Toppelberg, education in the United States retains a surprisingly tenacious notion that learning two or more languages somehow confuses or is detrimental to children. The problem, he says, is that the beneficial effects of bilingualism may diminish if a dual-language child is denied the support to master both languages.

"Most parents from well-to-do families recognize the benefits of learning two languages," says Toppelberg. "Why is it then that children from low-income, minority, and immigrant backgrounds are not afforded the opportunity to maintain and develop their own languages?"

Toppelberg studies how language development relates to mental health, particularly in dual-language children in socioeconomically disadvantaged circumstances. His concern is that these children will not only be at a communicative disadvantage, but also, because of that disadvantage, will suffer socially and economically. Bilingual proficiency, in contrast, opens the gates to a range of protective resources, both in a child's linguistic community and in the larger society, maximizing school engagement and success, and warding off depression, anxiety, and behavioral difficulties.

If allowed to blossom, dual-language children can thrive. Toppelberg, whose family is Spanish/English bilingual, illustrates this point by telling a story of when his son, then 18 months old, was following him around the house babbling in Spanish. As father and son walked outside so Toppelberg could talk with a contractor, the boy spontaneously switched to English, only to swiftly revert to Spanish when they moved back inside. "He did it," Toppelberg says, "because he knew at some level that he wanted to engage and learn from the contractor. The contractor would not understand him in Spanish. So he switched." ■

Susan Karcz is assistant editor of Harvard Medicine *magazine.*



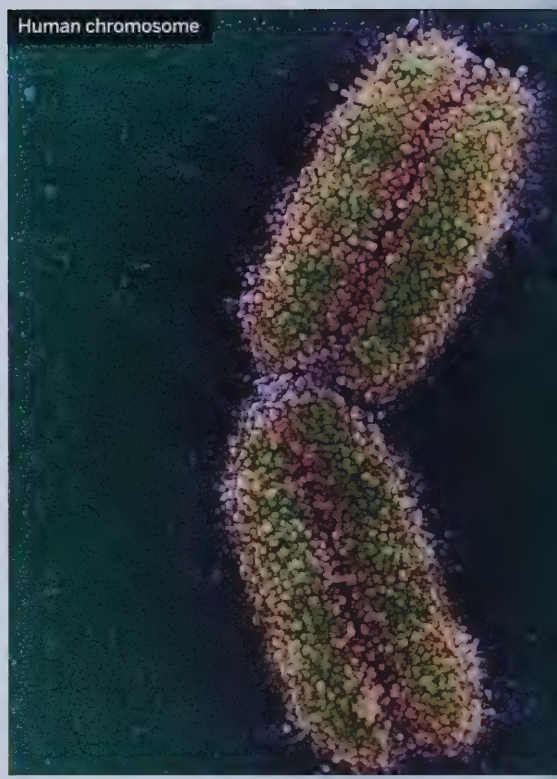
TETRA IMAGES/CORBIS

Secrets packed away in a family's genome are increasingly being found—and discussed
by David Cameron

legacy

Joseph Thakuria was facing an impasse. ■ He stood at a whiteboard in a conference room where a group of patients, all members of an extended family, sat around a table. They had come to him out of desperation. For generations, seemingly healthy family members in the prime of life had, without warning, died of a thoracic aortic aneurysm. The indiscriminate nature of the affliction was shaking the psychological well-being of the family tree. No one knew where they stood. Doctors were out of ideas. As a last-ditch effort to find answers, this band of relatives had come to Thakuria, a medical geneticist at Massachusetts General Hospital.

GOOD COUNSEL: Medical geneticists like Joseph Thakuria and Joan Stoler work with patients and their families as they learn of heritable conditions uncovered in analyses of the genetic information contained in their chromosomes.



JENNIFER SARBAHI (FAR LEFT); ADRIAN T. SUMNER/SCIENCE PHOTO LIBRARY

Using the investigatory skills that specialists like Thakuria are known for, part science and part detective work, he and his colleagues solved the mystery. Careful and intensive genome sequencing had fingered the causative mutation.

While knowing the identity of the genetic culprit would not point to a cure, it would allow physicians to screen family members. Those in the clear could breathe easy, while those bearing the DNA signature could take preventive measures.

Thakuria ushered the family into a conference room to explain all this—and to give each of them the option to be tested for the mutation. More than a dozen members of this extended family listened, rapt, as Thakuria described the diagnosis buried in their genes. Then, he asked each of them the million-dollar question: Do you want to know?

"Not everything in genetics is 100 percent certain and predictive the way it was for this particular family," says Thakuria, who also is an instructor in pediatrics at Mass General. "But there really is no correct answer to this question."

One by one, members of the family agreed to be tested. Then one said "no." He preferred to continue receiving annual echocardiograms rather than knowing which genetic cards he'd been dealt.

His relatives thought he was nuts. Each of them took him to task, insisting that there was only one sane answer to the question. Dodging the genetic test was simply not rational. In the hope of breaking the tension, Thakuria jumped in.

"I tried to explain that this was like deciding what to do with lottery money," he says. "It's different for everybody. There's no right or wrong."

The individual stuck to his decision, and, in the end, everyone was right. But what should medicine do when the patient is a family and the diagnosis implicates generations?

TRACY AIGUIER

The clinical use of genetic testing has caused an information surge that the medical establishment is struggling to manage.

A Change of Pace

Over the past decade, the science of genetics has accelerated at a rate that makes Moore's Law look like a slacker. Thanks to advances in technology platforms like microfluidics, printing out a patient's genetic code could soon become as routine as taking blood for a cholesterol test.

As Thakuria and his colleagues continue to incorporate more in-depth genomic sequencing into the clinic, researchers will need to grapple not only with a whirlwind of information, but also with patients and doctors who will struggle over how to interpret the results.

In short, the world of genetics is undergoing a revolution. But like all major cultural and technological insurgencies, the attendant issues raise a host of medical, social, ethical, and even psychological concerns.

Take Thakuria's foray into family therapy. Decades ago, the majority of known genetic disorders were rare, and often chromosomal. Today researchers know of nearly 5,000 such disorders. Not more than a decade ago, medical geneticists relied on physical examinations and phenotypic clues, while genetic testing yielded only the crudest data, confined primarily to single gene analyses and to locating large structural rearrangements, such as the extra chromosome that causes Down syndrome or the string of nucleotide repeats associated with Huntington's disease.

But the clinical use of genetic testing has now caused an information surge that the medical establishment is struggling to manage. Today, a person can spit into a tube, send the sample to any number of direct-to-consumer companies and, for as little as one hundred dollars, receive a scan of genetic markers—known variations in DNA that can be used to identify a person, species, or disease—that indicates susceptibility to conditions such as Alzheimer's disease and prostate cancer.

When We Talk About Genes

Joan Stoler knows well the complexity of translating genetic information to the layperson. For years, Stoler, an HMS assistant professor of pediatrics at Boston Children's Hospital and program director of the Harvard Medical School Genetics Training Program, has been working with patients and families as they wrestle with the fact that they carry a potentially troublesome genetic mutation.

One problem she and others in her profession confront is that for many conditions there is no definitive test. The binary precision of the genetic condition found in the family Thakuria was counseling isn't the norm. What's more, if genomic information has been increasing by an order of magnitude each year, so has our appreciation of a gene's complexity. Sure, a gene may be turned on or off—but it may also simply be dimmed. Or the gene itself might be fine but one of its regulators may have gone rogue. For unknown reasons, a genetic alteration that may result in a calamitous deformity in one person might cause a physiological blip in another.

In other words, as our knowledge increases, the one gene-one protein pedagogy becomes almost quaint.

Stoler, however, must explain the subtleties we do know about to her patients, finding ways to bridge the knowledge gap, and, often, a cultural gap.

"For a couple from China, who often have only one child, learning of a genetic defect is a tremendous blow," she says. "One mother, from Central America, thought the mutation her child carried occurred because when she was pregnant she wore red during an eclipse. Some blame coffee. Part of my job is simply to educate patients about what this all means. I try to drive home that each of us has something that we can pass down to our children."

Stoler often finds herself trying to explain the basic concepts of cells, chromosomes, genes, and proteins through an interpreter. In these situations, she goes visual, using charts, drawings, tic-tac-toe boards, and whatever analogies she can to inform those she is working with.

In a way, experts like Stoler play the traditional role of gatekeeper. They collect and interpret the genetic data, and then decide the best methods for educating the patient. But as genetic testing becomes increasingly democratized, how will the role of gatekeepers shift?

Green's Genes

Robert Green is an expert in moving genetic discoveries into genomic medicine. He has investigated and deciphered the nuances of many genomes, including his own.

Like Thakuria and Stoler, Green, an HMS associate professor of medicine at Brigham and Women's Hospital and director of the G2P (genomes2people) research program, is a medical geneticist. In addition to treating patients, he oversees a research program that can best be described as translational genomics. Green and his research colleagues use sequencing technologies to diagnose some of the more obscure conditions. But Green's discipline is complicated by some hazy intricacies. To illustrate this, he references his own genetic blueprint.

A full sequence of Green's genes turns up a few million variations, 109,000 of which could initially be considered medically relevant. Of these, computational analysis predicts that approximately 11,900 have an effect on a protein. Further analysis to find the variations that are uncommon, and thus more predictive of disease, leaves only 1,800. When this remnant is processed through a database of known genetic diseases, only 16 rare mutations are left.

UPON REFLECTION: A full sequencing of Robert Green's genome revealed 16 mutations that, without the benefit of clinical context, could be considered alarming.

Each of these 16 mutations could be alarming without clinical context. One of them, for example, is in the gene that causes Treacher Collins syndrome, a dominant condition resulting in severe facial deformities at birth. But here's the thing: Green doesn't exhibit a single feature of Treacher Collins. Which brings up yet another dilemma in the world of genetic diagnosis: There is no clear consensus on what defines a pathogenic mutation—and the race to package and sell translational software to patients and doctors may only add to the confusion.

"There's a powerful narrative in play that genomics will reveal all of our medical secrets, and that we all will benefit from genome sequencing," says Green. "But

There is, in fact, a great deal of angst in the medical community about how an increasing glut of genetic information will affect patient behavior.

there are many questions to be answered before genomics is routine, particularly in healthy individuals. Can we validate the interpretation of disease risks so that we know what the genome is telling us? Will genetic information improve people's health? How often is it misunderstood? Can it be dangerous?"

There is, in fact, a great deal of angst in the medical community about how an increasing glut of genetic information will affect patient behavior, and that is precisely what Green and his colleagues are studying.

Over the past decade Green has been the principal investigator for the REVEAL study: Risk Evaluation and Education for Alzheimer's Disease. For this project, researchers randomized participants to receive information regarding their genetic susceptibility to Alzheimer's.

"The study was run just like a clinical trial, except the drug we dispensed was genetic information," says Green.

The group measured potential patient harm in terms of anxiety, depression, and distress, eventually publishing in the *New England Journal of Medicine* that participants experienced a minimal and temporary rise in distress when they learned they were at an increased risk for Alzheimer's disease. Some of their subsequent behaviors were positive, such as better diet and more exercise; other behaviors were debatable, such as purchasing unregulated dietary supplements online. One striking finding: participants who learned that they were at increased risk reported increasing their long-term care insurance coverage.

For another set of participants, however, Green disclosed risk for heart disease along with the Alzheimer's risk and found that when people learned they were at risk for both conditions, they were, counterintuitively, less distressed.

"Our preliminary data suggest that learning about multiple risks, particularly if one of them seems preventable, is actually less distressing," he says.

In a separate study, Green and his group surveyed roughly 1,800 individuals who had received medically relevant genetic information through a direct-to-consumer company. When asked who they would present this information to, the respondents indicated overwhelmingly that they planned on discussing it with friends, family, and colleagues, and, in some cases, their family doctor. But few planned to discuss their results with a genetic specialist.

"As genomics enters the mainstream of medicine and society, regular physicians will have to learn to cope with this information about their patients," says Green. "Genetics is becoming democratized in a big way."

Green's newest studies are NIH-supported ones that will explore genomic sequencing in the medical care of adults and in newborns. Ultimately, this work anticipates a future where genomics data are available for every clinical visit.

Until then, medical geneticists are in the trenches with families excavating the uncertainties of inherited disease. Thakuria has continued to follow his family of patients. The good news is that, since availing themselves of genetic testing, no one in the family has died from the condition: screening and medical intervention has fended off what once seemed certain.

The kind of detailed sequencing that improved the family's options, however, is still reserved for extreme abnormalities. Thakuria, however, thinks that one day genomic sequencing will become a preventive measure, like mammograms and colonoscopies. If that occurs, family discussions of the results of genetic testing may lose some of their emotional freight. Then again, given family dynamics, maybe not. ■

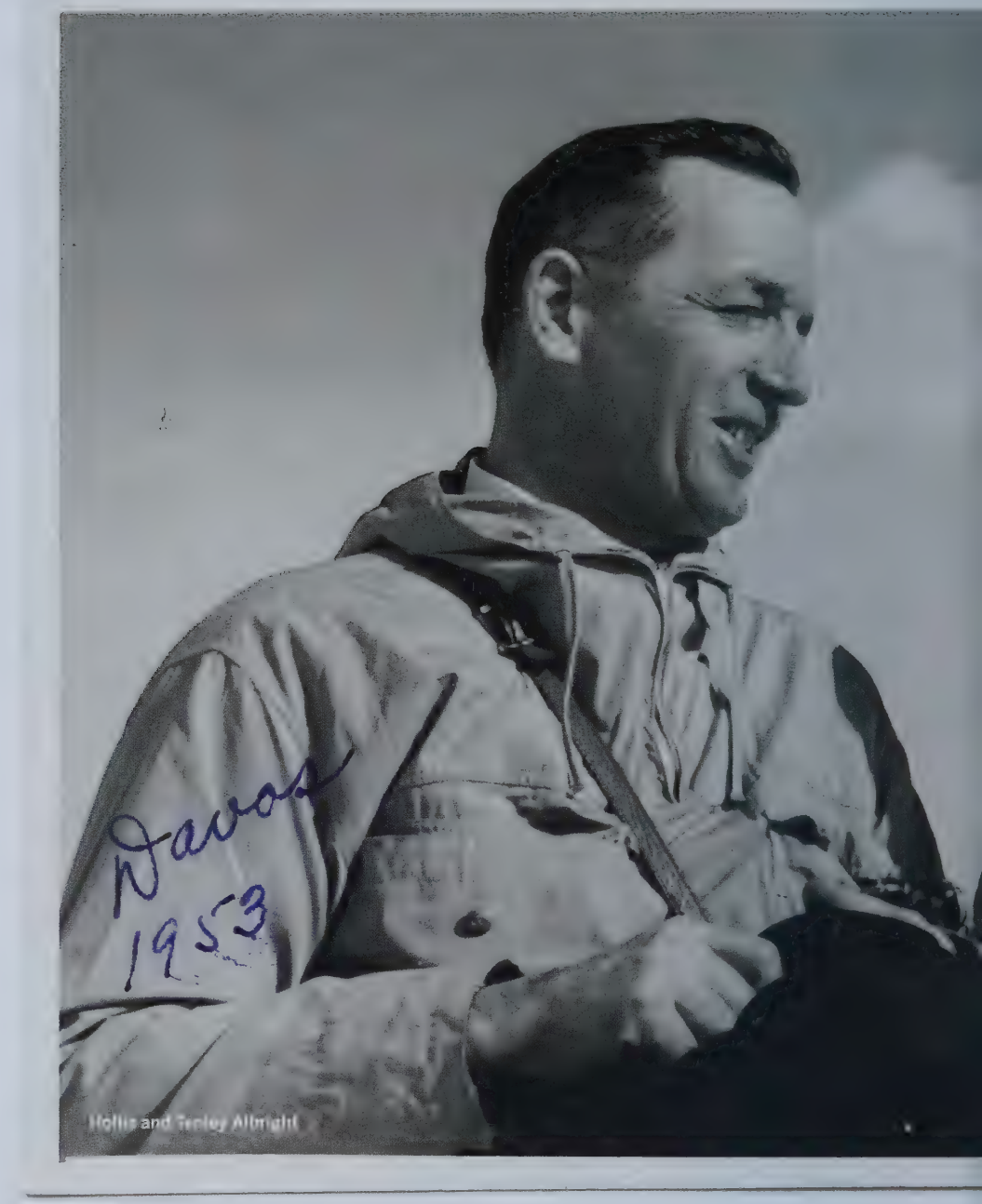
David Cameron is director of science communications in the HMS Office of Communications and External Relations.

Growing up with a doctor in the house makes a lasting impression

by Tenley Albright

What was it like growing up with a doctor in the house? ■ When I was asked this question recently, my immediate response was, "It was wonderful!" That would be my total summary of it. At the time, I didn't realize how wonderful it was. I knew my father, Hollis Albright '31, loved what he was doing. I like to say it was part of our daily life, and, in a sense, it was: Early in the morning, we would have breakfast together; he would then go off to work. ■ Some days, I would go with him to the hospital. When I was really little, I remember doing this and just loving the fact that I was going with him. I didn't see the patients. Instead, my father would leave me with the telephone operators at the front desk. I had a great time with them. »

MATTIAS PALUDI



COURTESY OF TENLEY ALBRIGHT

Later, as I was entering the profession, I remember leaning on his example. He wouldn't guide me by saying, "Do this or do that." Instead, I would learn how he thought by listening and by watching him work. I remember one time I was doing an appendectomy on a seven-year-old girl. He stuck his head in the door, saw what I was up to, and said, "Make the incision just where you would on Lilla." Lilla is one of my daughters, who was then six or seven years old. My first reaction was, "How could he say such a thing?" And then I realized he was telling me that every single case is just that personal, whether it is your daughter or someone else's daughter.

My father never pushed me to go into medicine. In fact, when I did apply to medical school I asked him, "Daddy, do you really not want me to apply to medical school?" "Oh, no, no, no," he said, "I just don't want to be the reason you made your decision."

My life benefited from the presence of my father, from my accompanying him to the hospital, from my being able to ask him questions about patients and caregiving, from my listening to—and still hearing—his encouragement and guidance. I know my behavior as a physician and surgeon has been shaped by the model he provided me.

But what about other children of physicians? What sorts of stories of the profession do other doctors have, especially others who, like my father and me, shared not only a family name and a profession, but also the experience of an education at Harvard Medical School?

To find out, I collaborated with the editor of this magazine and contacted other HMS alumni who are the children of HMS alumni. The sample is admittedly small and selected in a somewhat random manner. Despite that, the stories are amazingly similar, each illustrating the special bond that forms when a family shares not only home and history, but also profession.

Quentin, Claire, and Bradford Stiles

According to Bradford Stiles '89, his family could have opened its own hospital: "Dad was a cardiothoracic surgeon, Mom was an anesthesiologist, my older sister is a pediatrician, and an older brother is a general and trauma surgeon. I went into family practice and primary care sports medicine."

With a brother and a sister going through medical school while he was in high school, Brad had a good look at the profession before deciding to enter it. Exposure to hospital routines came from his parents, Quentin '55 and Claire '56. Quentin says he would occasionally take Brad on rounds on weekends, "when I just had to check on patients I'd operated on to make sure they were all right." Brad would hang out with the nurses and eat doughnuts. Brad's excursions with Claire had a different cachet: "When I knew there wouldn't be anyone at home, I'd take Brad to the hospital with me, stick him on a gurney, and either put him in the isolation room or in the lab, and let him blow spitballs on the ceiling." She adds, "Those spitballs are still there, by the way."

Ask Brad how his parents felt about their profession, and his answers show the power that early observations can have on

PODCAST

"Doppelgänger," a poem read by Elee Kraljii Gardiner, daughter of Tenley Albright '61
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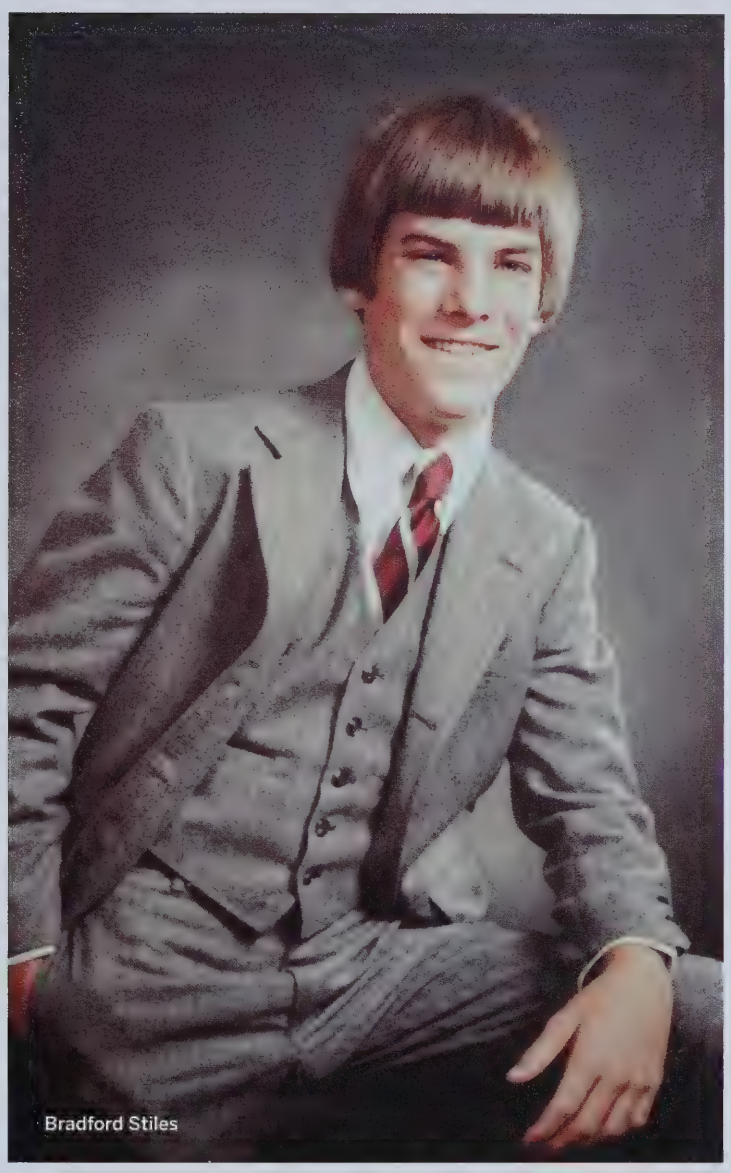


Bradford Stiles

COURTESY OF QUENTIN AND CLAIRE STILES

a life. "Dad was kind of on the early end of cardiothoracic surgery, so his skills were in demand. He wasn't home a whole lot: weekends, long nights, and evenings, he'd get home and within 10 minutes would get a call to return to the hospital. But having that kind of dedication and demeanor—how he would talk about the work—you could tell that he just really enjoyed what he was doing."

"When I was 12, I broke my arm," Brad says. "After it was set, I had intractable pain, went through a second surgery, and had some nerve damage. Mom took me with her to work every day—she worked in the county hospital then—and I got to watch her interact with patients and staff. I could see that she enjoyed her work."

The links remain strong among family members, and medicine remains a topic of family discussions. "It's been nice to have Claire be a physician," says Quentin, "because we could talk about medicine. Someone real close and real smart who could speak your language."

"Our family definitely has that common thread," says Brad. "We've always been very open. You can talk about anything, ask any question, bring up any problem. It was a good environment to grow up in."

Oni and Uché Blackstock

If you ask the Blackstocks, Oni '04 and Uché '05, whether their mother influenced their decisions to become physicians, be prepared to step back as these sisters pepper you with a litany of deeply felt reasons why their mother, Dale (Evans) Blackstock '76, was and remains a powerful role model in their lives, despite having died when the twins were 19 years old.

"We wanted to be just like her," says Uché. "We knew that she was very dedicated to her patients and that she really reaped a lot of joy from being a physician. It was impossible for that not to rub off on us."

"Uché and I grew up at the hospital with our mother," adds Oni. "We didn't consider doing anything else."

When the sisters were toddlers, Dale was doing a nephrology fellowship and spending long days on call at the hospital, so their father, Earl, would take them to the hospital to visit their mother. They also saw her

doing community health work throughout Brooklyn, where Dale had been born and reared. Whether in the hospital or the clinic, the twins always saw their mother as a person who derived happiness and satisfaction from her work.

They also saw a woman who looked life straight in the eye and navigated it with confidence and poise. "I think the lens through which we saw things was very different from what others saw," says Oni. "For us, having a mother who was a doctor was the norm."

"Our mother also drew upon and gave support to other women in the field," adds Oni. "She was president of an organization of black female doctors in Brooklyn. That was normal to us. We did, however, realize the sorts of obstacles she had to overcome to get to where she was."

The importance of support is not lost on Oni and Uché. They talk regularly and it's often about medicine. Oni conducts HIV research in women of color at Montefiore Medical Center, but also does clinical medicine, serving as a primary care doctor in the South Bronx. Uché is in emergency medicine at New York University, where she manages up to 25 patients during a shift and also teaches and supervises the hospital's residents and medical students. Both women have maintained a connection to their community and feel they are fulfilling an obligation to help people who are disadvantaged. Just as their mother did.

Jane Grayson, Anne Warren Peled, and Laura Warren

"We have a lot of friends who tell their kids absolutely not to go into medicine," says Jane Grayson '73. "They talk about medicine's terrible environment right now. But that's not how I feel. Yes, there are days when it's frustrating, but we both still love what we do."

The enthusiasm that Jane, a radiation oncologist, and her husband, a medical oncologist, have for their profession was never hidden from their daughters, Anne '07 and Laura '11.

"Looking back," says Laura, "I remember the joy that both my parents, but in particular, Mom, exuded about the work they did. Even though I didn't understand the nuances of Mom's job, I knew she was a doctor and that she felt she was making a difference."

Anne's recollections bring another dimension, "I think we always understood that, in their work, our parents were focused on treating people equally, and that they would go out of their way to make an effort to

ONLINE

Benjamin Greenberger '16 on his family's medical legacy
harvardmedicine.hms.harvard.

Laura and Anne Warren

Joan Martinez

Elena Martinez

1997. COURTESY OF JANE GRAYSON (ABOVE)

help others. I always knew this behavior also extended into the rest of their lives."

Outside of work, the busy parents were devoted to what was going on in Anne's and Laura's lives. Soccer games, school plays, rowing, all activities were supported—and attended by—their parents, despite what Anne calls their crazy schedules. "It was really all about us when they came home."

That focus was by design, according to Jane. "I always felt guilty because I worked full time and couldn't do the things that I had done with my parents. So weekends revolved around Anne and Laura and their interests, particularly their sports activities. Today, we go to scientific conferences to hear them present papers."

The bonds developed over the years hold the family close. What began as support for two young women and their myriad interests has grown and refined. This family of four is now scattered across the nation but is never apart. Daily telephone calls reinforce their ties as physicians and family.

"As a doctor," says Anne, "your work comes into your life in great ways. So when we get together, it's fun to talk about the things we've been doing at work. It's support that is hard to get anywhere else."

"Some might think we're boring," adds Laura. "We're all physicians. We're always talking about science and medicine. But when you share a passion and a lived experience, it's hard not to enjoy sharing it with a family member."

Joan Martinez and Elena Martinez Stoffel

When Joan Martinez '66, a pediatrician, moved to Honduras with her husband, a primary care physician, and three children under the age of two, she thought she might practice part time so that she could be with her growing family. But the constraints that came with practicing in a different country changed those plans.

Joan elected to stay at home and tend to three, then four, offspring; to informally care for the children of friends; to volunteer in orphanages, examining babies who were about to be adopted; and to work with Interplast, a charity of U.S. plastic surgeons who traveled annually to Honduras to perform reconstructive surgeries on indigent children.

"It was a fulfilling life," says Joan. "I felt connected to medicine even though I wasn't practicing."

That connection was one that daughter Elena '97 tapped into at an early age. "I was constantly exposed to what it was like to be a physician," she says. "My father would come home and discuss medicine with my mother, talking about patients he had seen that day. I grew up knowing what it was like to work in a hospital and to take care of patients."

"As far back as I can remember," she adds, "I wanted to be a doctor."

Following her residency, when Joan was working part-time for the city health department in New Haven, Connecticut, she would take Elena with her to clinic on days when the babysitter was sick. Joan credits those experiences with laying the groundwork for Elena's focus on medicine. "She must have incorporated the atmosphere, maybe learning to love the smells of the clinic."

Today, the child who sat in the clinic watching her mother examine other children is a gastroenterologist who also conducts research in cancer genetics.

Despite living far from one another, parents and daughter talk regularly, either through Skype or by phone. And their conversations always explore medicine. "We know exactly what's going on in her profession," says Joan.

Those conversations are as important to Elena as the dinnertime talks overheard between her parents. "It's exciting to be able to talk among ourselves about what we do. We understand—and appreciate—what one another does." ■

Tenley Albright '61, a former surgeon, is director of MIT Collaborative Initiatives in Cambridge, Massachusetts. Her collaborator on this article was Ann Marie Menting, editor of Harvard Medicine.

Three Coins from Freud

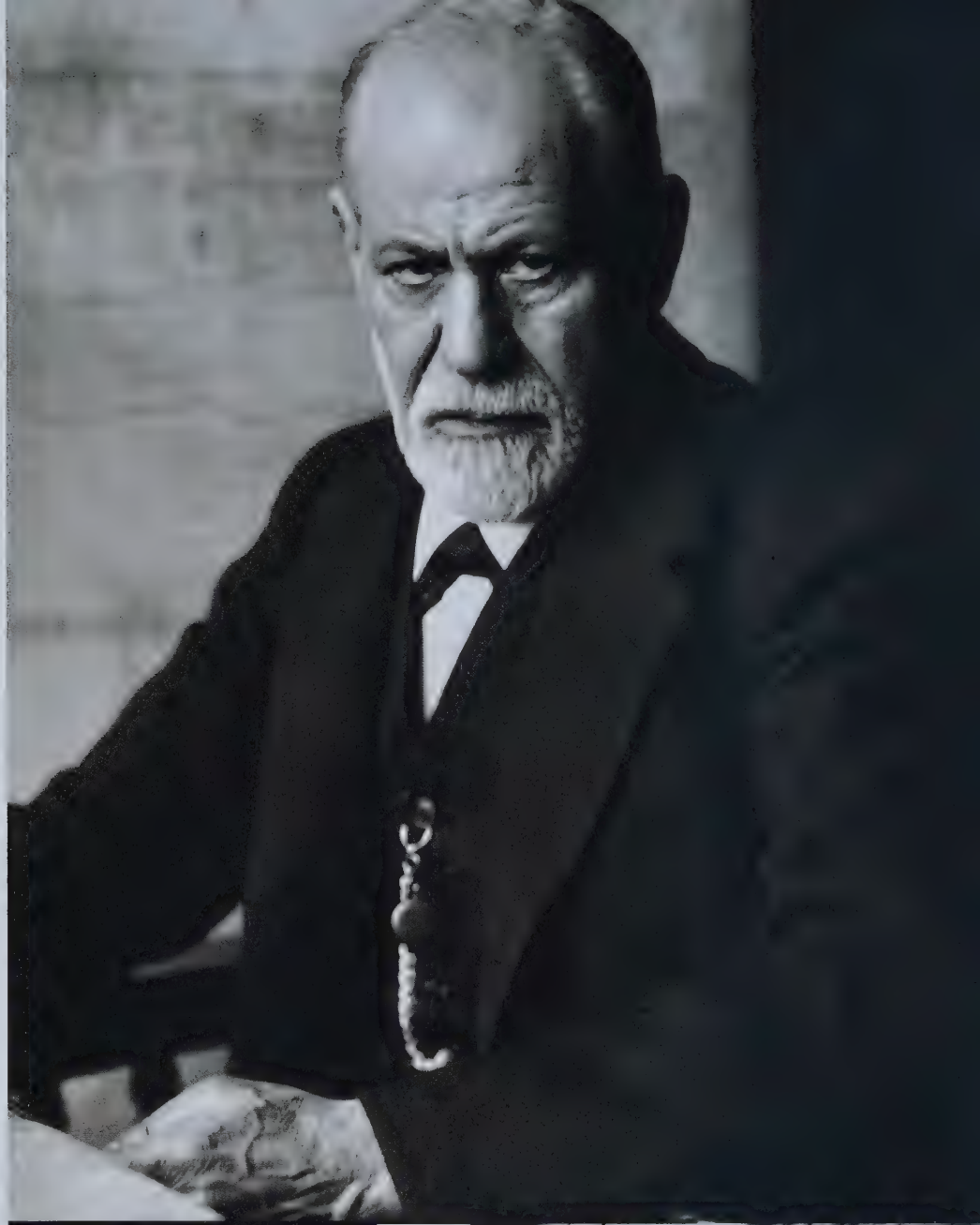
NEWLY MINTED: Sigmund Freud commemorated the author's birth by giving him three Austrian ducats similar to these circa World War I gold pieces.

A doctor–patient relationship spans nations, conflict, and generations

by Peter Schur

On May 6, 1933, my father, Max Schur, was examining Sigmund Freud. By this time, my father had served as Freud's physician for four years, overseeing his general care—Freud suffered from a heart condition—but especially monitoring and treating the oral lesions that plagued Freud. ■ My father had become Freud's physician after being recommended by Marie Bonaparte, the French author and psychoanalyst who was the great-grandniece of Napoleon. Bonaparte had been in Vienna undergoing psychoanalysis with Freud and had need of an internal medicine physician. Coincidentally, Freud also was in need of a physician; he had fired his personal physician after learning the man had kept from him the truth about the malignancy of his oral lesions. Thus, my father began a doctor–patient relationship that endured for 10 years, a decade that would turn out to be a tumultuous one worldwide. ■ On that day in May, however, Freud was marking his 77th birthday, and my father was awaiting the birth of his first child: me. My mother, Helen, herself a physician, was overdue, a fact that I'm told led Freud to urge my father to go to her side, saying, "You are going from a man who doesn't want to leave this world to a child who doesn't want to come into it." Three days later, I was born. In honor of my birth, Freud gave me three Austrian gold coins. »

Remarkably, I still have those coins. I've kept one. The others I've distributed to my two daughters, so that they each may have something to remind them of the Schur–Freud connection that, in its small way, helped shape history.



TIME AND PLACE: The pocket watch (left) that Sigmund Freud gave to Max Schur now resides with Freud's papers in the Library of Congress. Schur often met with Freud in his home in Vienna's Berggasse neighborhood, a location from which Schur may have hurried on the day his wife, Helen, gave birth to their son, Peter (opposite).

Sundered Lives

The world I came into, Vienna in 1933, was a world in turmoil. The day following my birth, for example, the newspapers reported the burning of Freud's works, an act justified as one "against the soul-destroying overestimation of the sex life—and on behalf of the nobility of the human soul."

In March of that year, neighboring Germany had placed Hitler in power and Nazism was on the rise. With that menace so near, many members of the Jewish population were fleeing, including Freud's sons and their families. Austria, weakened by a civil war incited by Nazi coalitions within the country, was allying itself with Italy's Benito Mussolini. In the unsettled period following the assassination of Austria's Chancellor Engelbert Dollfus, friends and family urged Freud and my father to leave. My father had gone so far as to apply for positions outside Austria, including one in Cairo. But Freud could not be persuaded, and my father, in deference to his patient, stayed. So did we.

In February 1938, Hitler handed Dollfus's successor, Kurt von Schuschnigg, an ultimatum: capitulate or be invaded. While Schuschnigg considered Austria's options, my father went to the U.S. embassy to

CONTAINER VA1, SIGMUND FREUD PAPERS: SIGMUND FREUD COLLECTION MANUSCRIPT DIVISION, LIBRARY OF CONGRESS, WASHINGTON, DC (FAR LEFT, OPPOSITE); FERDINAND SCHMUTZER, 1926 (ABOVE, OPPOSITE); UNKNOWN PHOTOGRAPHER, 1938 (BELOW, OPPOSITE). COURTESY OF PETER SCHUR

follow up on a visa application he had made the previous year under the Polish quota. My father had been born in 1897 in Stanislaw, a city that was then part of the Austro-Hungarian Empire but which had, in 1919, become part of Poland: thus, he was considered Polish. My father also urged Freud to leave. Freud refused. Soon it was too late for everyone: The German army invaded Austria on March 12 and annexed the country. The *Anschluss* had taken place.

The next few weeks were tense. My parents continued to go to work at the hospital and I to kindergarten. Many of our neighbors flew Nazi flags. There were parades. I remember my parents being afraid. In particular, I remember an episode when Nazis came to our house. I was on the steps leading upstairs. My father was asked about his possessions, and gave over his automobile; an unloaded, fancy revolver; and some gold coins. I was very upset about losing the car, for I remembered riding in it with my father during many pleasurable trips taken around Vienna.

As frightening as that visit was, my parents were thankful that nothing worse had happened. They knew of the concentration camps and exterminations in Germany. Their efforts to leave the country intensified. Soon, through the political connections of many, including Paris-based Marie Bonaparte, exit visas and permit papers for the Freuds, my family, and others were procured.

On June 4, we were about to leave for London with the Freuds when my father developed an acute severe phlegmonous appendicitis. The Freuds left, but we stayed while my father underwent an emergency appendectomy performed by an "Aryan" surgeon: At that time few Jewish patients

were admitted to hospitals and no Jewish physicians were allowed to practice in the hospitals. The Gestapo monitored my father closely; there were interactions between them and my father and mother at the hospital, at our home, and at Gestapo headquarters. Eventually, on June 10, we were allowed to leave. I remember my father arriving at the train station in a wheelchair, still bandaged, with a drain in his abdomen. The next day we arrived in Paris. We stayed there for three days while my father convalesced, then we traveled to London to join the Freuds.

BEGINNINGS AND ENDINGS: The birth of their son, Peter, brought joy to Max and Helen Schur (above) at a time when much of their world was poised for sorrow. A few years after Peter's birth, the Nazis invaded the family's beloved Vienna, propelling their efforts to flee to England and, ultimately, to the United States aboard the SS *President Harding* (far right, opposite).

Sea Change

In London, the routine between my father and Freud resumed. But Freud's malignant oral lesions recurred, and, in February 1939, a lesion developed that was deemed inoperable. After consultations, radiation therapy was begun.

Freud's end is well known and has been detailed by many. Early in their association, Freud had exacted a promise from my father that he would not allow Freud to die a tortured death. Freud now reminded my father of that conversation and asked him to fulfill his promise. My father consulted with Freud's daughter, Anna, and, on September 21, 1939, when Freud was again in agony, administered a one-third grain of morphine. His pain relieved, Freud fell into a peaceful sleep, then lapsed into a coma and died at 3 a.m. on September 23.

With Freud's death, my father's obligations to his patient were fulfilled, and we could join the masses of people fleeing Europe. In October, we obtained passage on the SS *President Harding*, sailing from Southampton, England, and stopping in France for additional passengers on its way to the United States. I slept on a cot in the ship's former drawing room with others, including my mother and my sister, Eva. My six-year-old self remembers our picking up survivors drifting in lifeboats following an attack by a German U-boat, and watching as British warships circled a burning vessel. I also remember that we were hit by a hurricane. From news reports I now know that one crew member died in that storm of October 17, and that 73 passengers and crew were injured, some severely. But I remember that right before the brunt of the storm hit, my mother performed an emergency appendectomy on one of the crew, with my father administering anesthesia, and the ship's doctor, fresh out of medical school, assisting.

When a tidal wave from the hurricane hit, I ended up under a pile of broken cots,

unscathed. I stayed in a corridor for a few hours wearing a life preserver as water occasionally swished around, and protecting Eva, as my parents attended to more than 100 fractures. The next night we all slept in one bed in a cabin. The next day a U.S. warship passed medical supplies to the ship via a line.

Bites of the Apple

In New York City, we moved first to the Hotel Anderson, at 80th Street and Columbus Avenue, then to 515 West End Avenue. I attended PS9.

My father resumed his private practice of internal medicine. He applied for hospital privileges and was told by all, except Bellevue Hospital, that they did not accept refugees or Jews. At Bellevue he became an internist in the Division of Syphilology and Dermatology. He renewed his interest in analysis and became a member of the British and New York psychoanalytic associations, eventually cofounding the Psychoanalytic Association of New York (Downstate).

In the late 1950s, he gave up internal medicine to practice analysis full time. He quit Bellevue and joined the Department of Psychiatry, Downstate NY Medical Center in Brooklyn, where he eventually became a clinical professor. In the late 1960s, he was president of the American Psychoanalytic Association.

My mother became affiliated with the Department of Orthopedics at Mt. Sinai Hospital in New York, where she eventually ran the polio unit, including the respirators, as well as the posture clinic, in the days before rehabilitation units. When vaccines vanquished polio, my mother switched careers and took a five-year residency in adult, child, and adolescent psychiatry at Downstate. This was followed by training in childhood and adolescent analysis. Before being required to retire by New York State (at age 85), she was an assistant professor of psychiatry. Until shortly before her death, my mother continued to see private patients and to work in a children's clinic in East Harlem.

In the fall of 1969, my father contracted the flu and possibly developed pneumonia. On October 12 of that year, he died in his sleep. My mother outlived him, and, collaborator to the end, wrote the preface to his book, *Freud: Living and Dying*, published in 1972.

Unbroken Links

The Schur–Freud connection lingers on in me. After graduating from elementary school, I attended Fieldston High School and went on to attend Yale College. In 1954, I entered Harvard Medical School, graduating in 1958. Anna Freud provided both Yale and HMS with wonderful, strong letters supporting my applications. During the years my father had cared for Freud, I had met Anna on several occasions. I recall her as a small, kind, fragile-looking lady.

In 1967, I joined the faculty at HMS, and, in 1978, became a professor of medicine at what is now Brigham and Women's Hospital. My clinical and research interests have focused on systemic lupus erythematosus. I have, over the years, become interested in the psychopathology of that disease and of illness in general. This, I suppose, is another way in which the Schur–Freud connection endures.

Much has been written about this connection, and I have often been asked, "What about the connection hasn't been told?" I can add nothing, for my father, as Freud's physician, was discreet about what could be said. If he felt something could not be said, he mentioned it to no one, neither my mother, myself, nor others.

I understand that. I feel that is the type of respect that all physicians owe their patients.

I am my father's son. ■

Peter Schur '58 is an HMS professor of medicine in the Department of Rheumatology and Immunology at Brigham and Women's Hospital.

HEADS AND TALES: Classic children's literature presents stories that entertain and educate; they are often accompanied by captivating illustrations such as this one by noted illustrator Jessie Willcox Smith. Titled "A Rainy Day," the illustration, which appeared in *Dream Blocks* by Aileen Higgins (New York, 1908), captures the spell that literature casts on young minds. Willcox Smith was recognized for her ability to portray children's worlds, as shown later in this article in her illustration for Robert Louis Stevenson's "The Land of Counterpane."

Childhood classics swathe familial illness, even death, in bravery, good deeds, and occasionally, magic

by Perri Klass

Fever Dreams

There are certain rashes so well evoked by their medical school taglines that the descriptions echo in your ears and come back to guide you in the exam room. Chicken pox: dewdrop on a rose petal. Erythema infectiosum: slapped cheek disease. Scarlet fever: sandpaper exanthem (go ahead—google "sandpaper rash" and see what you get). ■ A couple of decades ago, when I was relatively new to practicing, I saw a child with that sandpaper rash, and I asked the interpreter to explain to the child's Spanish-speaking grandmother that this was scarlet fever. I registered the rather lovely Spanish name of the disease when the interpreter spoke it: escarlatina. Then the grandmother started to cry.

was able to explain that we would treat with antibiotics and that the child would be fine. But I remember that grandmother's distress as a signal, a reminder that the easily treatable diseases of today can carry terrible memories from other times and other places. For me, that clinical moment was about the triumphant diagnostic click of recognizing the red sandpaper footprint of a toxin-mediated reaction to easily treatable group A strep. For the grandmother, it carried echoes of quarantine, serious illness, and even death.

It made me think back to the first times that I came across the words "scarlet fever" and to my earliest associations with the disease, way back before medical school, and even before college or high school. That introduction came as I read my way through the books that mattered most, the childhood classics that you read so closely and never forget.

The ways that classic works of children's literature encompass the illness—and sometimes the death—of pediatric protagonists tells us a great deal about both the realities of pediatric illness and the eternal verities of child-rearing and parenting. Childhood classics offer us a range of illness narratives, reminding us of dangers now preventable and treatable, but also of the universal imperatives of explaining, understanding, and accommodating the morbidity and mortality that still can go along with caring for children. Sickness in children's literature presents a huge and dramatically colorful range of plot twist, character development, moral challenge, tragedy, and triumph. Stories of sickness are also stories of tending and healing, of secret sickroom comforts, and of the love and care that comes from parents, from doctors and nurses, and from other children. As an adult, you might read with an eye to microbiology, but you will find yourself reading as well stories of family love, childhood resilience, and the glories of nature.

Once Upon a Time

What killed Beth in *Little Women*? No points if you said tuberculosis, although I know what made you think of it—Beth dies a slow but beautiful (and religious) death, wasting away, losing strength, and ultimately moving on to a better place. But the only diagnosis that author Louisa May Alcott gives us is the medical history: the case of scarlet fever that Beth contracts in the course of her faithful care of a family of poor German immigrants whom she and her sisters have taken on as objects of charity.

Beth gets very sick indeed. Alcott gives us descriptions of Beth's severe pharyngitis, her fever, and her delirium: "there came a time when during the fever fits she began to

COVER INSET FOR *ANNE OF GREEN GABLES*, LUCY MAUD MONTGOMERY (BOSTON, 1908); ILLUSTRATION BY HERMANN HETER FOR MARGARET SIDNEY, *FIVE LITTLE PEPPERS AND HOW THEY GREW* (BOSTON, 1881; FAR RIGHT)

Sickness in children's literature presents a huge and dramatically colorful range of plot twist, character development, moral challenge, tragedy, and triumph.

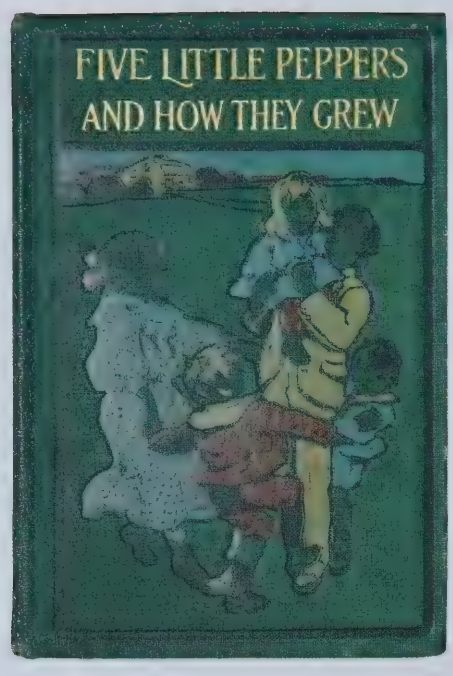
UNDER COVER: The stories of illness and death found in such children's classics as *Little Women*, *Anne of Green Gables*, and *Five Little Peppers and How They Grew* (left to right) temper the realities of pediatric illness with the strength and perseverance provided by family and friends.

talk in a hoarse, broken voice, to play on the coverlet as if on her beloved little piano, and to try to sing with a throat so swollen that there was no music left."

But Beth gets better. She almost dies of that scarlet fever, but she gets better. Or at least her family thinks she has recovered. The truth is, Beth is never really well again. She contracts the fever in chapter 17, and she recovers in chapter 18, but a couple of years later, she gets weaker and weaker, and finally she dies, in chapter 40. People reading the book from a medical point of view have speculated that Beth was left, after her bout with scarlet fever, with severe rheumatic heart disease, and that though the book doesn't explicitly make the connection, her frailty and progressive weakness were in fact related to the group A strep that caused her initial acute illness. In real life, Alcott's younger sister, Elizabeth Sewall Alcott, died on March 14, 1858, at the age of 22, just 2 years after recovering from scarlet fever, and 10 years before her sister published the book.

Beth's clinical course makes an interesting contrast with another literary case of scarlet fever. On the very first page of *By the Shores of Silver Lake*, set in 1879 and published in 1939 as the fifth book in Laura Ingalls Wilder's Little House series, we learn that the whole family had contracted scarlet fever. "Far worst of all, the fever had settled in Mary's eyes, and Mary was blind." And indeed, Wilder's older sister, Mary Ingalls, went blind at age 14, in 1879. In a recent issue of the journal *Pediatrics*, however, Beth Tarini and coauthors, in "Blindness in Walnut Grove: How Did Mary Ingalls Lose Her Sight?" showed that at the time, Mary's blindness was understood by her family to have been caused not by scarlet fever, but by brain fever, a colloquial term for meningoencephalitis.

Tarini told me that the origins of this article are rooted in her days as a medical student. During her pediatric clerkship, she said, she put up her hand during a discussion of scarlet fever and informed her attending that scarlet fever could cause blindness, and cited Mary Ingalls as an example. The attending had also read the Wilder books, Tarini remembers, but doubted the link between scarlet fever and blindness: "She couldn't resolve that with her own clinical experience." As Tarini went through her training in pediatrics, she also



noticed the disjunction between her modern medical perspective on scarlet fever and the fear that the term evoked for some parents. She completed the research while an assistant professor of pediatrics at the University of Michigan, drawing on her original medical student project and thinking not only about the pathophysiology of scarlet fever, but also about the power and influence of how we label illness and the cultural and historical context of disease.

Tarini and her coauthors speculate that Wilder's choice to attribute Mary's blindness to scarlet fever may have been a literary device employed for her young readers; she chose a common disease and a name that children would know in 1939 to account for a child going blind in 1879.

Thus, two classic children's books offer us two characters, both closely based on real girls, who suffered real illnesses: one who survives a case of scarlet fever, carefully described, and then goes on to die from what we would now understand to be post-streptococcal complications, and one whose blindness from a different infection is ascribed to scarlet fever as a useful well-known childhood villain.

Thus, two classic children's books offer us two characters, both closely based on real girls, who suffered real illnesses.

Literary Prescriptions

If you troll through the children's classics, you can find the whole infectious pantheon. Anne Shirley, the heroine of the 1908 book *Anne of Green Gables*, by Lucy Maud Montgomery, goes out to a neighbor's house to tend three-year-old Minnie May, who has bad croup, and "lay on the sofa feverish and restless, while her hoarse breathing could be heard all over the house." Anne, at the age of 11, knows what to do: boil lots of hot water and dose the child with ipecac. When the doctor finally arrives, she presents the case to him: "She got worse and worse. ... I actually thought she was going to choke to death. I gave her every drop of ipecac in that bottle, and when the last dose went down I said to myself. ... 'This is the last lingering hope and I fear, 'tis a vain one.' But in about three minutes she coughed up the phlegm and began to get better right away. You must just imagine my relief, doctor, because I can't express it in words. You know there are some things that cannot be expressed in words."

It's hard to know from the description whether Minnie May had what we would think of as normal croup—viral laryngotracheobronchitis—or whether she may in fact have had diphtheria. No one, however, seems worried about contagion, so perhaps diphtheria is less likely. Either way, ipecac was often used as an expectorant in cases of croup and bronchitis.

Diphtheria does show up in *Betsy-Tacy and Tib*, by Maud Hart Lovelace, published in 1941 but set at the turn of the twentieth century. Tacy, who is eight years old, develops the disease, and her family is quarantined: "'Quarantined' meant that they had to stay at home in order not to give anybody diphtheria. While Tacy was so sick they had to play quiet games, but now they could make all the noise they liked."

When Tacy is finally allowed out of quarantine, she has a serious discussion with her two best friends, Betsy and Tib. Betsy says, "We three ought to have something to remember each other by. You got sick, Tacy, and I might get sick too, any day. I might get sick and die." This is the prelude to a very funny scene in which the three girls cut off locks of one another's hair to stuff into their versions of Victorian memorial lockets, and, in the process, end up destroying Betsy's brown braids, Tacy's red ringlets, and Tib's yellow curls. But the book, written for and

LEAN ON ME: Children consoling children during illness and infirmity is a common theme in classic children's stories such as *Five Little Peppers and How They Grew*, in which older brother Ben helps sister Polly who, in turn, helps little sister Phronsie; *Little Women*, in which Jo stays by Beth's side as the younger sister fails, then dies; and *The Secret Garden*, in which cousin Mary and local lad Dickon bring wheelchair-bound Colin into a world of magic and hope.

PERCALE TO DREAM: The sickbed diversions offered by toys and imagination form the substance of "The Land of Counterpane," a poem (opposite page) by Robert Louis Stevenson, and the poem's illustration by Jessie Willcox Smith.

ILLUSTRATION BY JESSIE WILLCOX SMITH FOR ROBERT LOUIS STEVENSON, A CHILD'S GARDEN OF VERSES (NEW YORK, 1905)

The Land of Counterpane

When I was sick and lay a-bed,
I had two pillows at my head,
And all my toys beside me lay
To keep me happy all the day.

And sometimes for an hour or so
I watched my leaden soldiers go,
With different uniforms and drills,
Among the bed-clothes, through the hills;

And sometimes sent my ships in fleets
All up and down among the sheets;
Or brought my trees and houses out,
And planted cities all about.

I was the giant great and still
That sits upon the pillow-hill,
And sees before him, dale and plain,
The pleasant land of counterpane.

—Robert Louis Stevenson
A Child's Garden of Verses

about eight-year-olds, is perfectly willing to confront the possibility of sudden fatal childhood disease. In the first book in the series, *Betsy-Tacy*, Tacy's baby sister dies after an unnamed illness, and the five-year-olds seriously discuss heaven and the afterlife—and then move on to their next adventure.

If you want a really good literary case of measles, I would look to *Five Little Peppers and How They Grew*, Margaret Sidney's 1881 novel of New England family life. The poor but close and loving Pepper family is devastated by a bout of measles, explained by Mrs. Pepper as "something children always have," and which strikes down four of the five Pepper children. The one who is most dangerously ill is eleven-year-old Polly Pepper, the heroine of the book, whose eyes are threatened by the disease, so that her mother fears she will go "stone-blind." " 'My good woman'—Dr. Fisher's voice was very gentle; and he took the hard brown hand in his own—'your little girl will not be blind, I tell you the truth; but it will take some time to make her eyes quite strong—time and rest.'" So, poor Polly's eyes are bandaged, and she endures an interminable convalescence of darkness and inactivity: "Not to do anything! The very idea at any time would have filled her active, wide-awake little body with horror; and now, here she was!"

Unlike scarlet fever, measles is well known to cause blindness. Interestingly, malnutrition and vitamin A deficiency add to the risk; you might wonder whether the rather restricted diet of the impoverished Pepper family (mush for breakfast, potatoes for dinner) contributes to Polly's risk. But Dr. Fisher's prediction comes true, and Polly's eyes are eventually unbandaged, the measles vanquished, and the family restored to health.

Pint-sized Heroes

Classic children's literature gives us a look into the lives of children—at how the characters and the implicit audiences accommodated the very real knowledge of illness and death in times when most families were touched by serious childhood infections. It's striking how often, in children's literature, we see children taking care of other children, sometimes heroically, like Anne saving Minnie May, and sometimes by providing the day-to-day nourishment and distraction that helps a sick child recover. Polly Pepper, before she herself gets sick, tells her feverish little sister, Phronsie, funny stories about little chicks snapping up bugs to tempt her into taking one bite and then another of buttered toast; older brother Ben, when he recovers from his own bout of measles, tells wonderful tales to entertain poor Polly, with her bandaged eyes and her enforced idleness.

Sickrooms in these books are not necessarily terrible places. In *Little Women*, the whole March family takes loving care of poor Beth, once they have acknowledged that she cannot be cured: "The pleasantest room in the house was set apart for Beth, and in it was gathered everything that she most loved—flowers, pictures, her piano, the little worktable, and the beloved pussies. Father's best books found their way there, Mother's easy chair, Jo's desk, Amy's finest sketches, and every day Meg brought her babies on a loving pilgrimage, to make sunshine for Aunty Beth."

And when a child is left stricken—like Mary Ingalls—it is another child who helps her along. "On that dreadful morning when Mary could not see even sunshine full in her eyes, Pa had said that Laura must see for her." And Laura, almost 13 years old, takes on the responsibility, guiding her sister physically as the family moves west to the Dakota Territory, while also describing for her everything they pass, from landscapes to the construction of the transcontinental railroad.

Cast a Spell

There's a recurring theme in children's literature in which children, removed from adult supervision, act as saviors, rescuing one another, or even saving the world, says Maria Tatar, the John L. Loeb Professor of Germanic Languages and Literatures at Harvard University and an authority on children's literature.

As an example, Tatar points to the 1911 novel *The Secret Garden* by Frances Hodgson Burnett. In this work, Colin can leave his wheelchair behind and walk when he gets outside gloomy Misselthwaite Manor and goes into the hidden garden of the title, along with his cousin Mary and Dickon, the local boy who knows the secrets of the Yorkshire moors and the plants and animals that populate them.

When Tatar asked her students to read *The Secret Garden*, "the students fell in love with it," she told me. "Many of them knew it from childhood, but for many others it was this great discovery—the magical quality of that garden, the way the kids have their own little piece of real estate!" And in that magical piece of real estate, with no adults allowed, it is the children who take on Colin's illness.

Robert Louis Stevenson, who authored the 1885 poetry collection *A Child's Garden of Verses*, also was a sickly child; his diagnosis of tuberculosis has been debated in the medical literature, with suggestions ranging from bronchiectasis to hereditary hemorrhagic telangiectasia. Stevenson dedicated his collection of verses to the nurse who took care of him, Alison Cunningham: "For the long nights you lay awake / And watched for my unworthy sake: / For your most comfortable hand, / That led me through the uneven land." And then, from his adult perspective as one of the best known writers of his time, and as someone who had outgrown imaginary voyages taken during days of childhood sickness to wander the world over and write adventure stories, he wrote triumphantly to Cunningham: "From the sick child, now well and old / Take, nurse, the little book you hold!" ■

Perri Klass '86 is a professor of journalism and pediatrics and director of the Arthur L. Carter Journalism Institute at New York University.

Construction Site

RESEARCHERS AT HMS have developed new, complex three-dimensional structures they call bricks. Don't think you'll be able to build a house with them, though. These bricks are formed from self-assembled DNA strands.

Why use DNA?

"We like DNA because it is simple to design with, easy to program, and produces a robust structure," says Yonggang Ke, an HMS research fellow in biological chemistry and molecular pharmacology at the Dana-Farber Cancer Institute. Ke has worked on the project for the past two years.

DNA also holds a lot of information, a useful property when you want the molecule to direct itself into forming a desired complex structure. Getting molecules to configure themselves in useful ways is fundamental to the field of DNA structure technology, a form of molecular engineering that Ke pursues.

When the nucleic acids that make up DNA self-assemble into a single-stranded version of the molecule, the information they contain directs them to form what Ke and his colleagues refer to as a brick. Each brick is a modular unit, and like a LEGO block, it can connect to four neighboring bricks to form a module. Each of those four bricks is also capable of linking with neighboring bricks. Complex structures form as the number and position of modules vary. Think of a computer: small parts are assembled into larger components that interact with nearby sections in order to operate. So far in his work, Ke has been able to direct the bricks into more than 100 distinct shapes.

Ke, who works in the laboratory of Peng Yin, an HMS assistant professor of systems biology and a core faculty member of the Wyss Institute for Biologically Inspired Engineering at Harvard, says that although DNA structure technology has been around for 30 years, most of the designs produced by researchers are two-dimensional. But if researchers want to simulate biochemical reactions in cells, Ke says three-dimensional structures would be more useful.

"The most exciting thing for me is realizing this method enables us to make something much more complex than the two-dimensional structures we have," says Ke.

The technology has applications for biological and biomedical engineering. Ke sees drug delivery, biosensors, and tissue engineering as among the most promising biomedical applications. The bricks offer shape control and site-specific functionality—they can be put anywhere—characteristics that the team suspects will aid future applications.

—Katie DuBoff

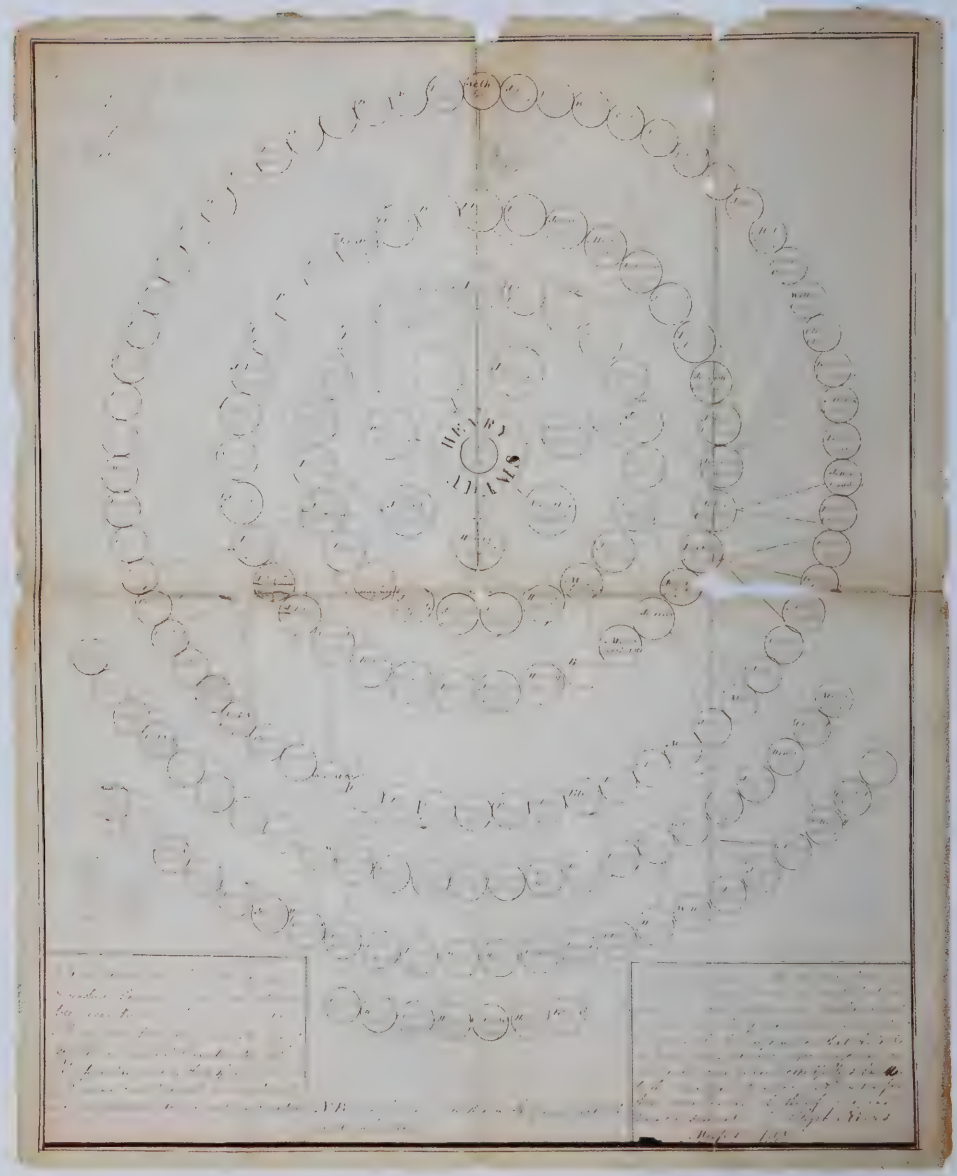
YONGGANG KE

FORM AND FUNCTION: DNA's useful properties, particularly its ability to hold large amounts of information, allow researchers to conceptualize a shape or function, program DNA molecules with the information needed to achieve the desired properties, and then let the molecules direct themselves to form the sought-after three-dimensional modular units known as bricks.

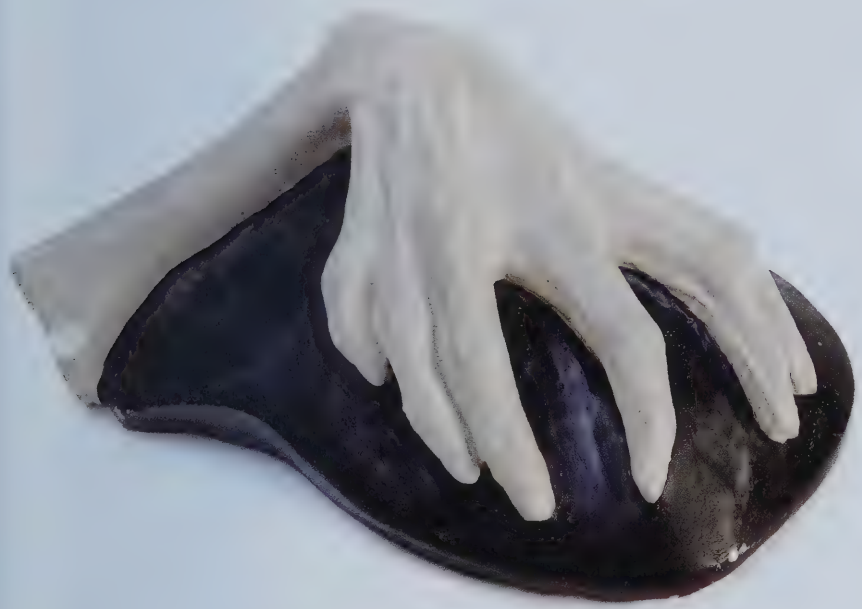
Habits, words and phrases, keepsakes, and, sometimes, even real estate, are the stuff family legacies are made of. The ubiquity of the phrase "leaving a legacy" hints at the wide acceptance of the concept of passing something on to the next generation.

Even medical schools rely on legacies. Among the several legacy-minded families to whom HMS owes its rich tradition—the Channings, the Shattucks, and the Bigelows, as examples—the Warren family stands out, for it is the one credited with building a foundation and structure upon which the School still relies. From John Warren (1753-1815) to his great-great grandson of the same name (1874-1928), five generations of Warrens handed to future generations of physicians not only medical knowledge, but also a school in which to pass that knowledge along. They also handed down more than 2,000 books, pamphlets, and manuscripts on medicine and surgery, a collection sufficient to start a library. Today, the collections of the Warren Library, a bequest of John Warren, Class of 1900, on his death in 1928, stand as one testament to this family's dedication to medicine and medical education.

—*Susan Karcz*



FAMILY PRACTICE: A genealogical chart (opposite) by Elijah Adams, circa 1798, traces the first family by the name of Adams in colonial America and includes three HMS graduates—each named Zabdiel Boylston Adams—from the classes of 1816, 1853, and 1903, Presidents John and John Quincy Adams, and patriot Samuel Adams; and a silver baby's rattle, presented to John Warren, Class of 1900, on his birth in 1874, by Benjamin Eddy Cotting. The engraving reads, "B.E.C. to J.W., the present to the future president, Mass. Med. Soc., Sixth Sept. A.D. 1874."»



Photographs of the three Guiteau siblings (clockwise from above), John, Charles (President Garfield's assassin), and Frances M. Scoville, circa 1882, meant to show how psychological tendencies manifest in facial features; two perspectives from a photograph album of J. Collins Warren showing images of family members, physicians, and others he encountered during travels in Europe; and a plaster replica of an adult hand and partial forearm, cast by Albert Franklin Sawyer, Class of 1852, showing seven well-developed fingers, indicative of an inherited condition known as polydactyly, or mirror hand, related to *Hox* gene expression.

Genealogical chart (a gift of Mitchell Adams) and hand cast courtesy of the Warren Anatomical Museum at the Francis A. Countway Library of Medicine. Photographs of C. Guiteau and siblings, bequest of Joseph Anton Denkinger to the Boston Medical Library at the Countway; and rattle, gift of Richard Warren, courtesy of the Boston Medical Library. Photograph album, bequest of John Warren to the Library of Harvard Medical School.

FIVE QUESTIONS

FOR DRAGANA ROGULJA

Assistant Professor of Neurobiology, Harvard Medical School

Why do you study sleep?
The problems I am drawn to are those that a five-year-old would be interested in (at least mine seems to be!). They are deceptively simple, so when you start scratching beneath the surface, other questions emerge that are unanswered and mysterious. I can't think of another behavior that's so familiar to all of us, yet harder to explain, than sleep.

What are you trying to understand?
We all think that we understand sleep, without thinking about it too much. We say "I sleep because I am tired." But what does that mean? Sleep is bizarre. For so many hours you are perceptually disengaged from your environment and from your internal states, so you can't tend to your offspring or to any of your own needs. You're vulnerable, you're seemingly unproductive. But as scientists we know there must be something productive underlying this behavior or it wouldn't happen. That's what I'm interested in understanding. Another basic question is how do you go from a state of awareness and cognition and emotion and engagement with the world to this state that in many ways resembles death but is quickly reversible?

What can fruit flies tell us about sleep in humans?
If you look at some of the genes known to regulate sleep, they are conserved between flies and us. Also, many of the pharmacological agents that regulate human sleep have the same effects in flies. Caffeine, for instance, arouses flies. We can relate to this, but most importantly that response suggests that the underlying molecular mechanisms of sleep regulation are conserved—and conserved mechanisms are what we want to study.

How many sleep genes are there?
We don't know. Sleep has been studied on an electrophysiological level in mammals, looking at brain activity during waking and sleep, but only recently have we had the tools to investigate genes directly related to sleep on a molecular level. So this is an exciting time for sleep research. I think we have an opportunity to make major progress in our understanding of this behavior in ways that were not possible before.

Are you confident we will learn why our awareness is extinguished when we sleep and reborn when we awaken?
I'm optimistic. In science I feel there's always an answer. It's not like trying to write a novel where you might not be certain what the endpoint should be. In science, you know things happen a certain way and that it can be difficult to figure out what makes it go that way. But there are ways to figure these things out. You just need to find them.

—Elizabeth Cooney

JOHN SOARES

President's Report

As a Quad "outsider"—a practicing obstetrician as well as a Californian—I'm excited about being the Alumni Council's president and having an opportunity to return to HMS and learn about the richness of the current student body and the faculty, and about our alumni, who represent diverse interests, geographies, and talents.

Bringing these groups closer together, and developing new avenues of volunteerism that alumni can tap to serve the public good, are the Council's core goals for the year ahead. Building on the program put in place by our past president, Nancy Rigotti '78, we will identify mutually beneficial initiatives that connect students with alumni across the nation. And we will look at ways HMS can provide learning, volunteer, and re-engagement opportunities to alumni across the country.

In my next report, I hope to share exciting new developments with you. In the meantime, I hope you will share your ideas with me at lauriegreenmd@gmail.com. It would be my privilege to hear from you.

Laurie Green '76 is an obstetrician and cofounder of Pacific Women's OB/GYN Medical Group in San Francisco.

MATTIAS PALUDI; ANGELA ALBERTI (FAR RIGHT)

A CRITICAL EYE

Second-year student takes a look at motherhood and medicine

BY THE TIME SHE WAS 14 YEARS old, Colleen Farrell '16 knew she wanted to be a doctor. But when she shared her career aspirations with a teacher, she was met with what would become a common question over time: How will you be able to practice medicine and raise children?

The question haunted Farrell, not only because it seemed discriminatory—no one asked this of aspiring male doctors—but also because she wasn't sure she could answer it. That uncertainty hasn't prevented Farrell from pursuing her dream of practicing medicine; instead, it spurred her to delve more deeply into the ethical considerations that face women who enter the profession.

Farrell, a former research assistant at The Hastings Center in New York State, was editor of the September 2013 issue of *Virtual Mentor*, the American Medical Association's online ethics journal. With a theme of motherhood and medicine, the issue opened with Farrell's editorial, "Motherhood and Medical Ethics: Looking beyond Conception and Pregnancy."

"Within bioethics, when we talk about gender issues, it's usually related to reproduction. The issues surrounding conception, abortion, and new technologies to treat infertility have captured the public interest. They get talked about a lot," Farrell says. "I wanted to think of motherhood and reproduction in ways that extended beyond biology."

Bioethics and medical ethics encompass the study of moral principles and implications related to the clinical care of others, but, says Farrell, "we don't research the ethics of motherhood, and that is the ultimate caring relationship." With each article she selected, Farrell attempted to shed light on what she calls "the day-to-day ethical dilemma that, in a way, we're all participating in"—that is, the issues surrounding motherhood.

Those issues range from the exclusion of pregnant women from drug trials, to the mothering experiences of the incarcerated, to the effect of global migration on mothering and caregiving.

"Social structures like incarceration or migration shape people's experiences of motherhood," says Farrell. "Physicians are encountering women in these vulnerable situations—in the role of both mother and patient—and I think it's important to be mindful of that."

—Angela Alberti

LIFE CHANGING: Children in Vietnam who have disfiguring birthmarks can receive treatment for vascular anomalies at a clinic set up by Thanh-Nga Tran and colleagues.

PERFECT VESSEL

Alumna recognized for establishing a vascular anomalies center in Vietnam

IN 2008, WHILE SERVING as a medical volunteer in her native country of Vietnam, Thanh-Nga Tran '00 was struck by the staggering medical and social needs of children with disfiguring birthmarks from hemangiomas and other vascular anomalies.

"Many hemangiomas ulcerate during their growth phase, causing severe pain and increasing the risk of infection and scarring," says Tran, an HMS clinical instructor in dermatology at Massachusetts General Hospital. "Aside from the potential physical disability, psychosocial problems can occur in children who are forced to live with a facial deformity during the formation of their initial self-image."

Tran's concerns were heightened by the realization that these children lacked access to modern health care and often received outdated treatments that can lead to further disfigurement.

The experience inspired Tran to start a free clinic to treat children with vascular anomalies and to begin a program for educating Vietnamese physicians about modern treatments for the anomalies.

Working with a team of collaborators from the United States and a dermatologist in Vietnam, Tran cofounded the first vascular anomalies center in Ho Chi Minh City in 2009.

"The goal is to have the Vietnam Vascular Anomalies Center closely model treatment centers in the United States, where difficult cases that require multidisciplinary efforts are discussed among member physicians and treatment options are outlined," says Tran.

Over the past five years, the center has evaluated more than 2,000 children and treated more than 700. It has also established an affiliation with the Ho Chi Minh City University of Medicine and Pharmacy, which has facilitated international collaboration in teaching and research.

Tran and cofounder Richard Anderson '84, an HMS professor of dermatology at Mass General, have launched a clinical trial in collaboration with colleagues in Vietnam to assess whether early treatment of hemangiomas can prevent their subsequent growth and reduce the potential for disfigurement in affected children. They also are investigating ways to reverse radiation dermatitis with the goal of helping children who have been scarred by radiation.

In recognition of her efforts in Vietnam, Tran was recently named as one of seven members of the HMS community to receive a 2013 Dean's Community Service Award, sponsored by the HMS Office for Diversity Inclusion and Community Partnership.

COURTESY OF THANH-NGA TRAN

A Change of Heart

Albright Symposium honors fourth-year student

SLATED FOR SURGERY: Sophia McKinley (center), who plans to become a surgeon, received the 2013 Hollis L. Albright MD '31 Scholar Award from Tenley Albright (left), Jeffrey S. Flier, George Daley, and Nile Albright at the annual Albright Symposium.

WHEN SHE WAS A FIRST-YEAR MEDICAL student, Sophia McKinley '14 thought she was "too nice" to be a surgeon. Surgeons were mean, cynical, and pessimistic, she believed.

Now a fourth-year student at HMS, McKinley is applying to residency programs in general surgery, her ideas about the specialty having been transformed by her yearlong experience with the HMS Cambridge Integrated Clerkship.

It was there that McKinley learned how a surgeon can provide healing and compassion to patients through meaningful relationships that last well beyond the one day spent in the operating room.

"At the heart of surgery is the care of the patient," McKinley told more than 100 people who gathered on October 16 in the Joseph B. Martin Conference Center for the annual symposium honoring Hollis Albright.

"Surgery's true nature is a merciful and compassionate endeavor. I dream of a future in which more students at Harvard enter surgery because of their compassion, not in spite of their compassion," McKinley said.

McKinley was honored with the 2013 Hollis L. Albright MD '31 Scholar Award for her achievements in neuroscience research as well as her community service as an HIV counselor and as a volunteer in homeless shelters. Following her third year at HMS, McKinley completed a master of education program at the Harvard Graduate School of Education so that she could acquire the tools to assess and improve the surgical training of medical students.

Tenley Albright '61, lecturer on surgery at Beth Israel Deaconess Medical Center and director of MIT Collaborative Initiatives, warmly praised McKinley before summing up the world of medicine the young award winner is entering as "a difficult, challenging time in health care, but an inspiring time of scientific discovery in the life sciences."

Albright, an Olympic gold medalist in figure skating, and her brother Nile, himself a champion speed skater before also becoming a surgeon, fondly recalled the example their father set, one that encouraged them to follow him into the field of surgery.

The symposium's moderator was George Daley, HMS professor of biological chemistry and molecular pharmacology at Boston Children's Hospital. Keynote speakers were Lewis Cantley, HMS visiting professor of medicine at Beth Israel Deaconess Medical Center and director of the Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital, and Peter Sorger, the Otto Krayer Professor of Systems Pharmacology at HMS and director of the newly formed Harvard Program in Therapeutic Science (HiTS).

—Elizabeth Cooney

CLASS NOTES

NEWS FROM ALUMNI

1945

Martin Lubin

I'm still on faculty at Geisel School of Medicine at Dartmouth, and still looking for a way to test a proposed novel treatment for incurable tumors that lack a specific gene. These tumors would include those developing from pancreatic, lung, brain, breast, and prostate cancers; melanomas; acute leukemias; and lymphomas. In 2011, along with colleagues at the Robert Wood Johnson Medical School and the Southern Research Institute, I published promising results on this effort in a mouse model in *Cancer Biology and Therapy*.

1949 65th REUNION

Thomas Hall

I finally received my AB from Harvard College in 2013, 73 years after starting it in 1940. I was the oldest graduate in the class, and may be the oldest student to have received an AB from the College. My education was interrupted; I was jailed for 13 months for refusing to serve in World War II, but was re-admitted to Harvard and received my medical degree. During the past four years, I have enjoyed taking my final four required classes by special arrangement while living in the State of Washington.

1954 60th REUNION

Gerold Schiebler

I was awarded the Distinguished Achievement Award from the University of Florida in May. My wife, Audrey, and I were honored by the State of Florida by being named to receive the Lawton Chiles Advocacy Award in April. We're looking forward to the 60th reunion in 2014.

Nanette Wenger

I've received the prestigious Arnall Patz Lifetime Achievement Award from the Emory Medical Alumni Association. It is awarded to an outstanding, compassionate physician and teacher who is also a leader at the Emory University School of Medicine and in the greater community.

1955

Thomas Daniel

My new book, *Times and Tides of Tuberculosis*, recounts the evolving perceptions of tuberculosis in the words of those who have been affected by the disease. It's scheduled for publication at the end of October by Fithian Press, an imprint of Daniel & Daniel Publishers.

1961

Newton Hyslop, Jr.

I'm leaving New Orleans after 29 years to return to Massachusetts. My 27 years as chief of the infectious disease section at Tulane University Health Sciences Center spanned the beginning of the AIDS epidemic in the Gulf South and allowed me to participate in the national effort to discover treatments for infections and, ultimately, for HIV itself. During my tenure there I was also honored to receive the Spirit of Charity Award in 2010 from the Medical Center of Louisiana Foundation for services rendered and for the teaching of students, residents, and fellows in keeping with the mission of Charity Hospital.

1963

Stephen Howard

My wife, Clare, and I moved to Florida nearly two years ago; she loves it, and I'm getting used to it. Initially, I worked with BayCare Health System, but after almost a year, I determined it was consuming my life. I'm now working with Gulf Coast Counseling Center, which is a lot more manageable. The best things about living in Florida, besides being near family, are bicycling on the Pinellas Trail, the beaches, spectacular cloud formations and golden sunsets, and having a pool right in your own back yard! The worst things include the wild drivers and the heat. That list doesn't include hurricanes because we haven't had a real one yet. As they used to say on TV: "C'mon down!"

1964 50th REUNION

Robert Reynolds

I retired from the University of Virginia in 2008, a tenure that included seven years as vice president of information technology, but was called back a year after retiring to implement our new electronic medical record system. After 18 months on that project, and witnessing its successful launch, I retired a second time in 2010—this time for good. My wife and I just celebrated my 75th birthday by traveling to France for three weeks. Other than dealing with a chroni-

cally ailing back, life goes well for me and our four children (no grandchildren so far). Hope to see many of you at our 50th!

1967

Tom Dunham
Since retiring from my internal medicine practice three years ago, I have been a volunteer physician teaching Palestinian medical students and house staff at a historic hospital in East Jerusalem. This has been a most rewarding endeavor for me both culturally and professionally.

Thomas Gutheil
I was selected as 1 of 10 U.S. professors to receive a Beckman Award in 2013. The award, conferred by the Elizabeth Hurlock Beckman Trust, honors professors who inspire their former students to make a difference in the community. In November, I joined my corecipients in Atlanta for the award ceremony.

Philip Landrigan
Since 2010, I have had the pleasure of serving as dean for global health at the Icahn School of Medicine at Mount Sinai in New York.

1974 40th REUNION

Thomas Najarian
I continue to work part time as a consultant to Vivus Pharmaceuticals, Inc., which acquired my medical invention and named it Qsymia, now an FDA-approved drug for weight loss. My development of this product began in 1999; I'm pleased it is now being marketed in the United States.

1975

Jennifer Puck
I received the 2013 Abbott Award in Clinical and Diagnostic Immunology from the American Society for Microbiology.

Reed Pyeritz
I've been named the William Smilow Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania, where I am also professor of genetics and the vice chair for academic affairs in the Department of Medicine.

1978

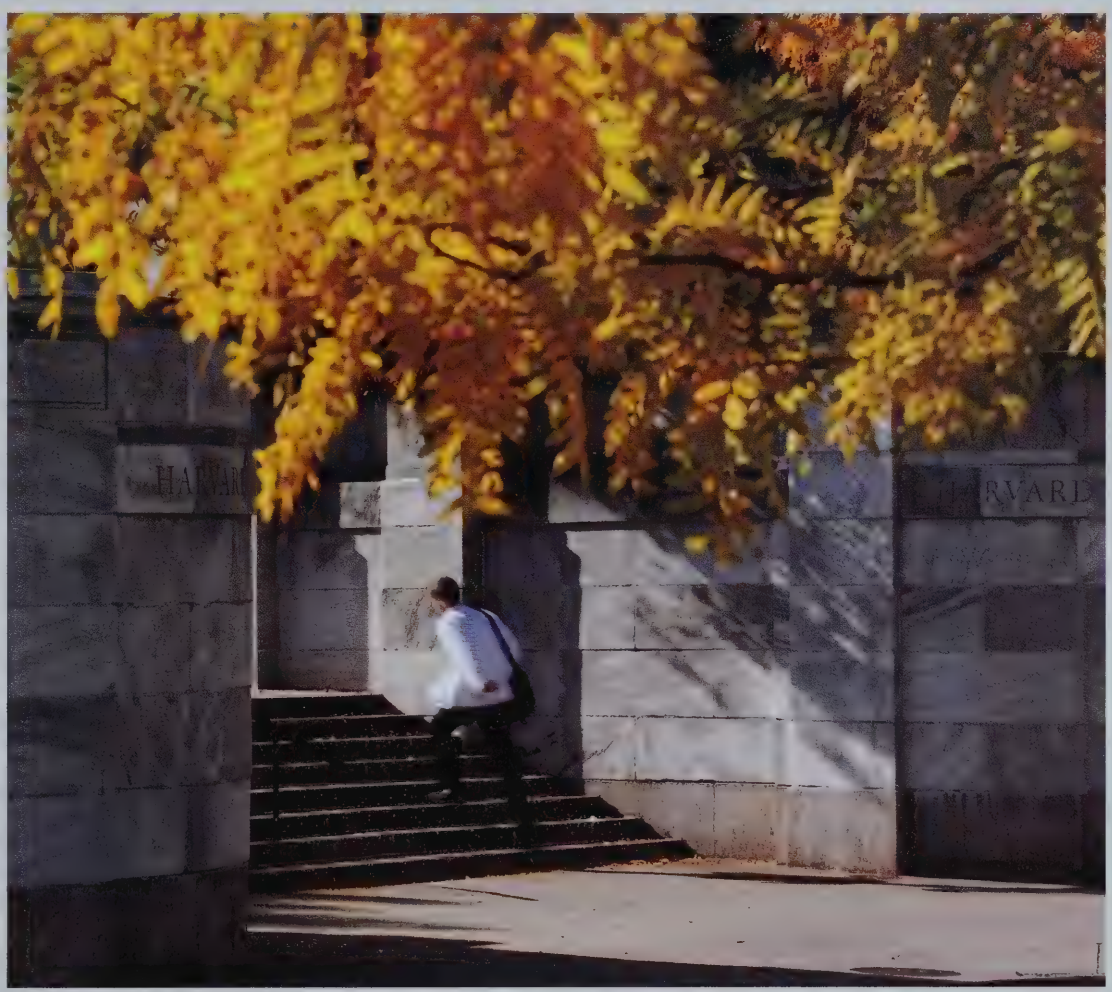
Katherine Murray-Leisure
Both children are launched, and my granddaughter in Atlanta has taken her first steps into my arms. I'm fortunate to be back in New England, closer to the rest of my family. During off hours, I enjoy kayaking, windsurfing, neighbors on our local beach, church choir, winter ski tours, and celebrating four generations of family affairs.

1982

Joseph Schifilliti
I'm growing into my role as a risk manager at the Southeast Permanente Medical Group in Atlanta. The work is new to me and challenging.

1983

Hugh Calkins
I've been elected president of the Heart Rhythm Society, an international organization of specialists in heart rhythm



CLASS NOTES

NEWS FROM ALUMNI

disorders from 72 countries. I was elected during the organization's 34th Annual Scientific Sessions in Denver.

Stephen Chanock
I've been appointed director of the National Cancer Institute's Division of Cancer Epidemiology and Genetics. I took over from the Division's founding director, who stepped down in 2012.

1984 30th REUNION

Stephanie Taylor
I finally gathered the courage to start my own company. It is terrifying, but has been well worth the effort. Since receiving a master's in architecture in 2007, I have been designing hospitals, and, in the process, developed an interest in health care-associated infections. So, two years ago I started a consulting company that focuses on decreasing the transmission and reservoirs of these bugs. Meanwhile, my pride and joy, Colin, is attending the Geisel School of Medicine at Dartmouth, and plans a career in clinical medicine and health care delivery optimization. I still live in Stowe, Vermont, with my husband and six dogs. Lots of room here so come and visit.

1990

Christopher Senkowski
I was appointed chair of the Department of Surgery at the Mercer University School of Medicine in Savannah, Georgia. I have been professor of surgery and program director for the general surgery residency program at Memorial University Medical Center in Savannah since 2011.

1993

Nathan Selden
I'm president-elect of the Congress of Neurological Surgeons. **Karen (Hedges) Selden** and our three kids are wonderful. The oldest, now a 14-year-old high school freshman, is taller than I am!

2000

Laura Meeks Saltonstall
I have joined the Board of Trustees of The Boston Home, a residence and care center for adults with advanced multiple sclerosis and other progressive neurological diseases. Since 2004, I have been the senior medical director, and head of global communications, strategy, and tactics for MS medical affairs at Genzyme Corporation.

2006

Sachin Jain
The first issue of *Healthcare: The Journal of Delivery Science and Innovation* has launched! It features introductory notes from **Don Berwick '72** and **Jim Kim '86**; an interview with **Mark McClellan '89**; and original research from leading health services researchers. I cofounded the journal with Amol Navathe, and **Ashish Jha '96** serves as one of our senior editors-in-chief.

2010

Maya Anantha Babu
I've been elected to the American Medical Association's Board of Trustees.

Share Your News

If you have updates you'd like to share in Class Notes, you can now submit them easily and securely to classnotes@hms.harvard.edu. Be sure to include your full name and class year.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1930s

1939

Elbert T. Rulison, Jr.
September 12, 2013

1940s

1942

James Eugene Lewis, Jr.
July 27, 2013

Edward E. Moore
August 15, 2013

1943

William H. Daughaday
May 3, 2013

Bruce A. Harris, Jr.
August 28, 2013

Roger W. Morrison
June 23, 2013

1944

Bernard Becker
August 28, 2013

Robert Paine
June 16, 2013

1945

Reginald H. Fitz
May 28, 2013

Charles F. Morrell
August 18, 2013

John M. Packard
July 12, 2013

1946

James H. Averill
August 3, 2013

Harold G. Johnson
September 10, 2013

David H. Solomon
July 9, 2013

1947

Clinton Piper
September 20, 2013

Harold C. Spear
August 29, 2013

Morton N. Swartz
September 9, 2013

1948

Ernest Mond
September 2, 2013

Arthur I. Ortenburger
August 4, 2013

1949

Shirley M. Gallup
August 2, 2013

1950s

1950

John C. Dalton
June 23, 2013

1952

Susanne J. Learmonth
August 31, 2013

1953

Harold J. Simon
August 6, 2013

1954

Kenneth R. Briggs
June 10, 2013

Herbert M. Matthews
June 6, 2013

1955

Arthur J. Deikman
September 2, 2013

Jonas M. Goldstone
September 7, 2013

1956

Peter Reich
August 11, 2013

1957

Peter R. Huttenlocher
May 15, 2013

1958

Peter D. Alden
September 23, 2013

Lewis R. Weintraub
August 18, 2013

1960s

1963

Peter T. Franck
June 28, 2013

1966

Carlton M. Akins
June 9, 2013

1969

Thomas S. Freeman
July 21, 2013

1970s

1970

Philip H. Wade
June 11, 2013

1975

Stephen P. Kelleher
June 22, 2013

Maryellen M. Rybak
July 20, 2013

1980s

1983

Linda A. Fay
September 30, 2013

1984

Jane C. Weeks
September 10, 2013

1990s

1996

Keith D. Amos
June 17, 2013

2000s

2004

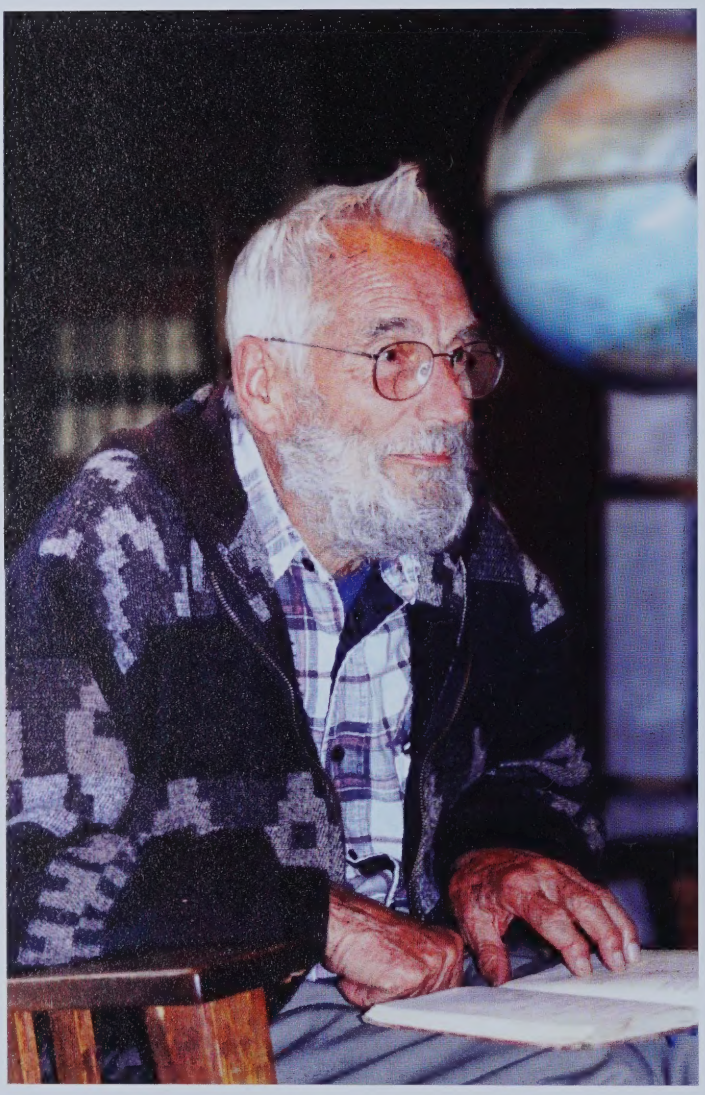
Jeremy S. Tucker
September 6, 2013

This listing of deceased alumni and their dates of death include those alumni whose notices of death were received between June 14, 2013, and October 11, 2013. Links to full obituaries of these alumni can be found at hms.harvard.edu/memoriam.

If you know of an HMS alumna/us who has died recently, please send an email with the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF JOHN CANDLER COBB



CLAIMS TO FAME: Professor, Department of Preventive Medicine and Comprehensive Health Care, University of Colorado School of Medicine; former Chairman, Department of Preventive Medicine, University of Colorado School of Medicine; author, *Fragments of Peace in a World at War*.

IN FOCUS: The cablegram that changed John (Jock) Cobb's life came in 1944, during World War II, when he was in Italy. A Quaker and a conscientious objector, Cobb '48 had volunteered with the American Field Service as an ambulance driver. Although Cobb belonged to a family of physicians, he had resisted becoming a doctor himself. But his experience as an ambulance driver changed his mind, and he applied to HMS while a volunteer. "The doctors were the ones who were trying to put things back together. Everybody else was trying to tear it apart," says Cobb. On the day the cablegram arrived, Cobb and his platoon were preparing to provide medical support to soldiers who would be involved in a tank battle. "A motorcyclist came up from headquarters," says Cobb, "and handed me a cablegram that said I had been admitted to Harvard Medical School. I just couldn't believe it. I didn't even think I was going to live until the next day." He stuffed the cablegram in his pocket—and found it there more than two weeks later after being hospitalized for jaundice caused by exposure to hepatitis A.

DEPTH OF FIELD: Following graduation from Harvard College, Cobb became involved with the Religious Society of Friends. The tenets of Quakerism have since shaped his life: In addition to his CO status during World War II, he participated in earthquake relief work in Mexico with the American Friends Service Committee. As the Korean War loomed, he went to New Mexico to serve in the Indian Health Service, which he credits with launching his public health career.

BEYOND NEGATIVES: After graduating from HMS, Cobb moved up the ladder of academia. His first appointment was at Johns Hopkins School of Medicine. Later, after moving west, he eventually became chair of the Department of Preventive Medicine at the University of Colorado in Denver. During his sabbaticals, Cobb would work as a maternal and child health consultant with international groups such as the World Health Organization and USAID. His wife and their four young children often accompanied him.

THE MOMENTS OF A LIFE: Cobb's life has been rich and ranging—and he's documented it all in pictures. He remembers receiving his first Kodak camera at the age of six. That gift led to a lifelong hobby that included a stint as the photography editor of the *Harvard Crimson*. Cobb took his camera around the world, documenting his work in northern Africa, Pakistan, Taiwan, Tibet, Turkey, and Turkmenistan. His camera also went with him to war. "I had a box about the size of a large typewriter in which I carried everything I needed to develop film in the absence of modern facilities," he says.

Cobb's negatives from his wartime photography sat in a shoebox for 60 years until he and his son Nathaniel '84 sorted through them. In 2011, some of those images appeared in Cobb's book, *Fragments of Peace in a World at War*.

—*Katie DuBoff*

ALAIN-PIERRE L'LOT

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Elee Kraljii Gardiner, daughter of Tenley Albright '61, reads "Doppelgänger," her poem inspired by medical school stories heard from her mother and grandfather.

Benjamin Greenberger '16 carries on his family's HMS tradition, begun by his grandfather and continued by his father and eight uncles.

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